Safety Assessment of *Zingiber officinale (*Ginger*)* – Derived Ingredients as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	November 10, 2021
Panel Meeting Date:	December 6 – 7, 2021

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer, CIR.

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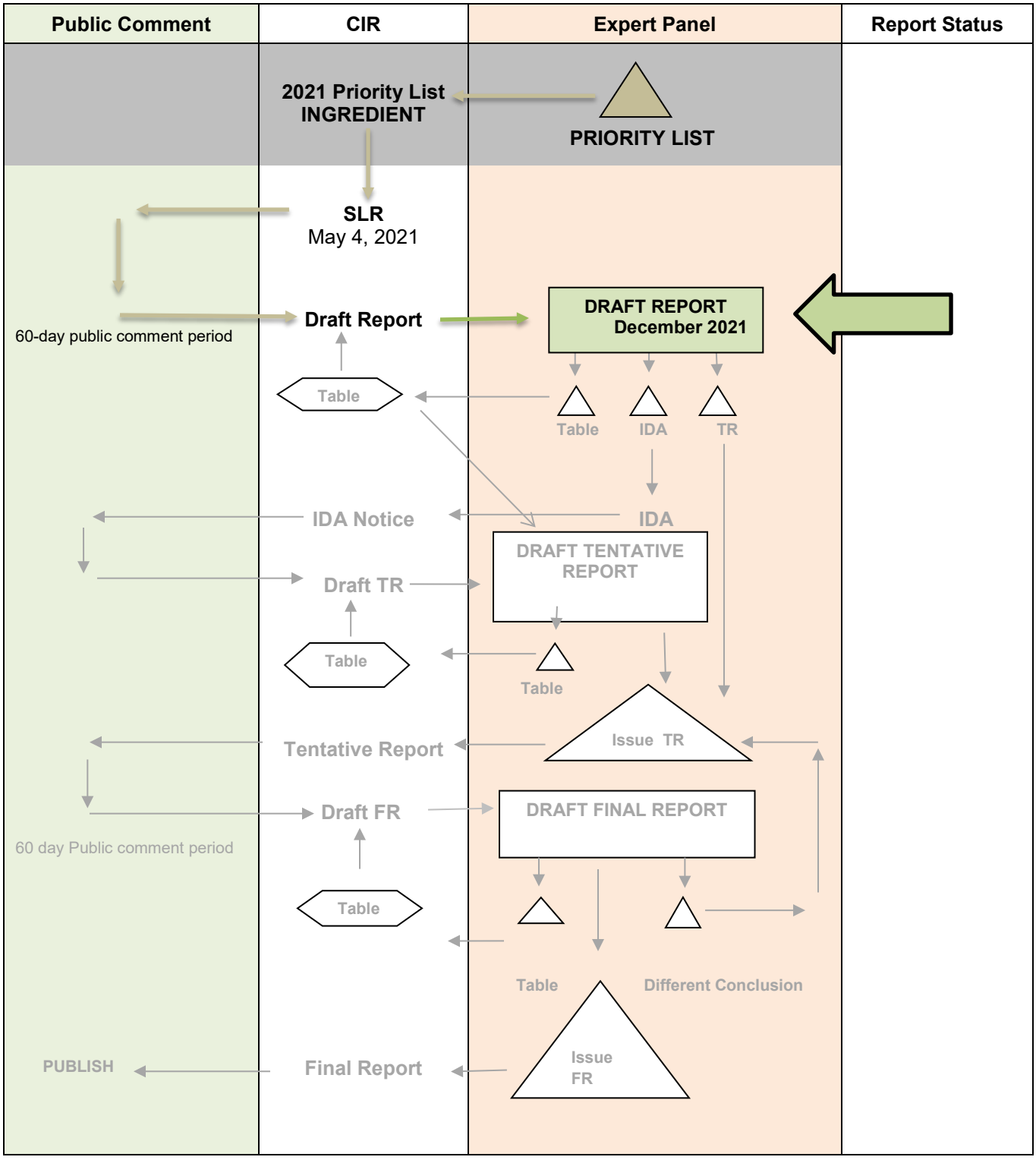
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Zingiber officinale* (ginger)-derived ingredients

MEETING December 2021



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Scientific Analyst/Writer, CIR
Date: November 10, 2021
Subject: Safety Assessment of *Zingiber officinale* (ginger)-derived ingredients

Enclosed is the Draft Report of the Safety Assessment of *Zingiber officinale* (ginger)-Derived Ingredients in Cosmetics (*report_Ginger_122021*). The following 9 *Zingiber officinale* (ginger)-derived ingredients are reviewed in this report:

Zingiber Officinale (Ginger) Extract
Zingiber Officinale (Ginger) Leaf Cell Extract
Zingiber Officinale (Ginger) Rhizome Extract
Zingiber Officinale (Ginger) Root
Zingiber Officinale (Ginger) Root Extract
Zingiber Officinale (Ginger) Root Juice
Zingiber Officinale (Ginger) Root Oil
Zingiber Officinale (Ginger) Root Powder
Zingiber Officinale (Ginger) Water

This is the first time the Expert Panel is reviewing this ingredient group. The Scientific Literature Review (SLR) was announced on May 4, 2021. Since the issuing of the SLR, the following unpublished data were received.

- Repeat insult patch test; 104 subjects; serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract; Anonymous 2015 (*data1_Ginger_122021*)
- 48-h occlusive patch test; 10 subjects; product containing 0.0995% Zingiber Officinale (Ginger) Root Extract; Anonymous 2012 (*data1_Ginger_122021)*
- Repeat insult patch test; 53 subjects; product containing 0.2% Zingiber Officinale (Ginger) Root Extract; Anonymous 2018 (mentioned in data1_Ginger_122021 memo, but full study details are presented in *data2_Ginger_122021)*
- Manufacturing information on Zingiber Officinale (Ginger) Water (*data3_Ginger_122021)*
- Ingredient breakdown of Zingiber Officinale (Ginger) Water (*data3_Ginger_122021)*
- Manufacturing information on Zingiber Officinale (Ginger) Root Extracts; Anonymous 2021 (*data5_Ginger_122021*)
- Manufacturing information on a trade name mixture containing 12 - 17% Zingiber Officinale (Ginger) Root Extract; Active Micro Technologies 2015 (*data5_Ginger_122021)*
- Composition information of a trade name mixture containing 12 - 17% Zingiber Officinale (Ginger) Root Extract; Active Micro Technologies 2021 (*data5_Ginger_122021)*
- Specifications of a trade name mixture containing 12 - 17% Zingiber Officinale (Ginger) Root Extract; Active Micro Technologies 2018 (*data5_Ginger_122021)*
- In vitro dermal and ocular irritation assays on a trade name mixture containing 12 - 17% Zingiber Officinale (Ginger) Root Extract; Active Micro Technologies 2014 (*data5_Ginger_122021)*
- In chemico skin sensitization assay on a trade name mixture containing 12 - 17% Zingiber Officinale (Ginger) Root Extract; Active Micro Technologies 2015 (*data5_Ginger_122021)*
- In vitro skin sensitization assay on a trade name mixture containing 12 - 17% Zingiber Officinale (Ginger) Root Extract; Active Micro Technologies 2016 (*data5_Ginger_122021)*

Included in this packet are concentration of use data (*data6_Ginger_122021*), 2021 VCRP frequency of use data (*VCRP_Ginger_122021*), report history (*history_Ginger_122021*), data profile (*dataprofile_Ginger_122021)*, search strategy (*search_Ginger_122021*), and flow chart (*flow_Ginger_122021*). In addition, comments on the SLR from the Council, and responses to those comments, are attached (*PCPCcomments_Ginger_122021; response-PCPCcomments_Ginger_122021).*

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: June 1, 2021

SUBJECT: Scientific Literature Review: Safety Assessment of *Zingiber officinale* (Ginger)-Derived Ingredients as Used in Cosmetics (release date May 4, 2021)

The Personal Care Products Council has no suppliers listed for Zingiber Officinalis (Ginger) Root Juice.

The Personal Care Products Council respectfully submits the following comments on the scientific literature review, Safety Assessment of *Zingiber officinale* (Ginger)-Derived Ingredients as Used in Cosmetics.

Key Issues
For published studies on ginger-derived ingredients throughout the report, please provide information on how the ingredient was prepared.

Cosmetic Use – Aerosol shaving products are not considered an inhalation risk in the categorization of FDA product categories for the summary of use information in CIR reports.

Additional Considerations
Introduction – It should be noted that skin protectant and antimicrobial agent are considered drug functions in the United States.

Introduction – Rather than stating that "potential toxicity from exposures to mixtures of different chemical compounds may not replicate the biological activity of the individual compounds", it should state that the "biological activity of individual compounds may not be the same as the effects of the mixture".

Method of Manufacture, Zingiber Officinale (Ginger) Root Extract – Please correct "pieced" to "pieces"

Composition and Impurities, Zingiber Officinale (Ginger) Root Extract – Please identify the "various solvents" that were used to make the root extract. A table showing the composition of the extracts prepared using different solvents would also be helpful. Ash is not actually "present" in samples, it is what is left after a sample is burned and includes the metals that were measured.

Penetration Enhancement, Summary – A p value ≥ 5 does not make sense as an indication of statistical significance. The abstract of the paper says "($p \geq 0.05$)" which also does not make sense as generally statistical significance is indicated if p is ≤ 0.05. Please check this paper again as the statistics, at least as presented in the abstract, are questionable. Perhaps, the actual differences in penetration should be presented in the CIR report rather than the statistics.

ADME – In the human study (reference 33), it would be helpful to state all the compounds for which the analysis was completed.

Short-Term, Human – Serum enzyme levels are not generally considered "hematological parameters". Please revise this to "hematological and biochemical parameters".

Anti-Reproductive Toxicity Studies – It would be helpful to include more information about these studies, such as the endpoints examined and any information on the mechanism of action.

UV Protective Effects – Reference 17 also looked at UV protective effects *in vitro* in HaCaT cells, and looked at the effects of the ginger components, gingerol, and shogaol. This information should also be presented in the CIR report.

Immunomodulatory Effects, Zingiber Officinale (Ginger) Rhizome Extract – Please revise: "assays were performed the individual patients' sera"

Summary – Please correct: "were given were given up"

Table 1 – As the CIR report mentions both a fixed and essential ginger oil, it would be helpful to note in this table that the chemical class for Zingiber Officinale (Ginger) Root Oil in the Dictionary is essential oils and waters.

Table 3 - In the title of this table, please indicate if this is an essential oil. It would also be helpful to include a total row to see how much of the oil was accounted for by the components that could be quantified.

Ginger-derived ingredients - December 2021 – Priya Cherian	
Comment Submitter: Council **Date of Submission: June 1, 2021**	
Comment	**Response/Action**
For published studies on ginger-derived ingredients throughout the report, please provide information on how the ingredient was prepared.	general methods of preparation for these ingredients can be found in the method of manufacturing section
Cosmetic Use – Aerosol shaving products are not considered an inhalation risk in the categorization of FDA product categories for the summary of use information in CIR reports.	Addressed
Introduction – It should be noted that skin protectant and antimicrobial agent are considered drug functions in the US.	Addressed
Introduction – Rather than stating that "potential toxicity from exposures to mixtures of different chemical compounds may not replicate the biological activity of the individual compounds", it should state that the "biological activity of individual compounds may not be the same as the effects of the mixture"	Addressed
Method of Manufacture, Zingiber Officinale (Ginger) Root Extract – Please correct "pieced" to "pieces"	Addressed
Composition and Impurities, Zingiber Officinale (Ginger) Root Extract – Please identify the "various solvents" that were used to make the root extract. A table showing the composition of the extracts prepared using different solvents would also be helpful. Ash is not actually "present" in samples, it is what is left after a sample is burned and includes the metals that were measured.	Addressed
Penetration Enhancement, Summary – A p value ≥ 5 does not make sense as an indication of statistical significance. The abstract of the paper says "($p \geq 0.05$)" which also does not make sense as generally statistical significance is indicated if p is ≤ 0.05. Please check this paper again as the statistics, at least as presented in the abstract, are questionable. Perhaps, the actual differences in penetration should be presented in the CIR report rather than the statistics	Addressed
ADME – In the human study (reference 33), it would be helpful to state all the compounds for which the analysis was completed	Addressed
Short-Term, Human – Serum enzyme levels are not generally considered "hematological parameters". Please revise this to "hematological and biochemical parameters"	Addressed
Anti-Reproductive Toxicity Studies – It would be helpful to include more information about these studies, such as the endpoints examined and any information on the mechanism of action.	These were briefly summarized as they are not typically included in CIR reports.
UV Protective Effects – Reference 17 also looked at UV protective effects in vitro in HaCaT cells, and looked at the effects of the ginger components, gingerol, and shogaol. This information should also be presented in the CIR report	Addressed
Immunomodulatory Effects, Zingiber Officinale (Ginger) Rhizome Extract – Please revise: "assays were performed the individual patients' sera"	Addressed
Summary – Please correct: "were given were given up"	Addressed
Table 1 – As the CIR report mentions both a fixed and essential ginger oil, it would be helpful to note in this table that the chemical class for Zingiber Officinale (Ginger) Root Oil in the Dictionary is essential oils and waters.	Addressed
Table 3 - In the title of this table, please indicate if this is an essential oil. It would also be helpful to include a total row to see how much of the oil was accounted for by the components that could be quantified	essential oil clarified in title

Zingiber officinale (Ginger)-Derived Ingredients – History

February 2021

- Concentration of use received for ingredient group

May 2021

- SLR posted
- Data received:
    - Repeat insult patch test; 104 subjects; serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract
    - 48-h dermal irritation assay; 10 subjects; product containing 0.0995% Zingiber Officinale (Ginger) Root Extract
    - Repeat insult patch test; 53 subjects; product containing 0.2% Zingiber Officinale (Ginger) Root Extract
    - Manufacturing information on Zingiber Officinale (Ginger) Water
    - Ingredient breakdown of Zingiber Officinale (Ginger) Water
    - Manufacturing information on Zingiber Officinale (Ginger) Root Extract
    - Composition information on Zingiber Officinale (Ginger) Root Extract
    - Specifications on a Zingiber Officinale (Ginger) Root Extract
    - In vitro dermal and ocular irritation assays on a Zingiber Officinale (Ginger) Root Extract
    - In chemico skin sensitization assay on a Zingiber Officinale (Ginger) Root Extract
    - In vitro skin sensitization assay on a Zingiber Officinale (Ginger) Root Extract

June 2021

- Comments on SLR received

December 2021

- Panel reviews DR

***Zingiber officinale* (ginger)-derived ingredients Profile – December 2021 – Writer, Priya Cherian**																															
				Toxicokinetics			**Acute Tox**			**Repeated Dose Tox**			**DART**		**Genotox**		**Carci**		**Dermal Irritation**			**Dermal Sensitization**				**Ocular Irritation**		**Clinical Studies**	
	Reported Use	**Method of Mfg**	**Impurities**	**log P**	**Dermal Penetration**	**ADME**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**In Vitro**	**In Vivo**	**Dermal**	**Oral**	**In Vitro**	**Animal**	**Human**	**In Vitro/In Chemico**	**Animal**	**Human**	**Phototoxicity**	**In Vitro**	**Animal**	**Retrospective/ Multicenter**	**Case Reports**
Zingiber Officinale (Ginger) Extract	x	x		x				x			x				x				x			x				x			x
Zingiber Officinale (Ginger) Leaf Cell Extract																														
Zingiber Officinale (Ginger) Rhizome Extract	x	x						x			x			x															
Zingiber Officinale (Ginger) Root																														
Zingiber Officinale (Ginger) Root Extract	x	x	x		x	x					x								x	x	x	x		x		x			
Zingiber Officinale (Ginger) Root Juice		x																												
Zingiber Officinale (Ginger) Root Oil	x	x									x				x															
Zingiber (Ginger) Root Powder	x	x	x					x			x			x																x
Zingiber Officinale (Ginger) Water		x																												

* "X" indicates that data were available in a category for the ingredient

Zingiber Officinale (Ginger)-Derived Ingredients

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Zingiber Officinale (Ginger) Extract	84696-15-1	yes	yes	no	no	no	no	yes	yes	yes	no	no	no	no	yes	no	yes
Zingiber Officinale (Ginger) Leaf Cell Extract		yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Rhizome Extract		yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Root		yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Root Extract	84696-15-1	yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Root Juice	84696-15-1	yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Root Oil	8007-08-7	yes	yes	no	no	no	no	yes	yes	no	no	no	no	no	no	no	yes
Zingiber (Ginger) Root Powder		yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes
Zingiber Officinale (Ginger) Water	84696-15-1	yes	no	no	no	no	no	no	yes	no	no	no	no	no	no	no	yes

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	AHPA	AGRICOLA	IFRA	RIFM
Zingiber Officinale (Ginger) (general)	84696-15-1	yes	yes	yes	no	no	no	no	no
Zingiber Officinale (Ginger) Extract		no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Leaf Cell Extract		no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Rhizome Extract		no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Root		no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Root Extract	84696-15-1	no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Root Juice	84696-15-1	no	no	no	no	no	no	no	no
Zingiber Officinale (Ginger) Root Oil	8007-08-7	no	no	no	yes	no	no	no	no
Zingiber (Ginger) Root Powder		no	no	no	yes	no	no	no	no
Zingiber Officinale (Ginger) Water	84696-15-1	no	no	no	no	no	no	no	no

Search Strategy

-the search terms below were used to search for this ingredient group; if useful information were found in the links above, a "yes" is noted

Typical Search Terms

- CAS numbers
- INCI names
- Ginger
- Zingiber officinale
- Zingiber safety
- Ginger food
- Ginger case report
- metabolism
- dermal
- inhalation
- skin
- toxicity
- drugs
- medicine
- irritation
- ocular
- eye
- sensitization
- allergy
- manufacture
- cancer
- carcinogenicity
- mutagenicity
- Ames
- Reproductive
- Teratogenicity
- Synthesis

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse

- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/phytochem/search
- Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – https://ifrafragrance.org/
- Research Institute for Fragrance Materials (RIFM) - https://www.rifm.org/#gsc.tab=0

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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer, CIR.

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ABRREVIATIONS

ALP	alkaline phosphatase
AST	aspartate aminotransferase
BAL	bronchoalveolar lavage
BUN	blood urea nitrogen
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
DART	developmental and reproductive toxicity
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DNFB	dinitrofluorobenzene
DPPH	1,1-diphenyl-2-picryl-hydrazyl
DPRA	direct peptide reactivity assay
ECHA	European Chemicals Agency
FDA	Food and Drug Administration
GC	gas chromatography
GD	gestation day
GRAS	generally recognized as safe
HaCaT	human epidermal keratinocyte line
HDM	house dust mite
HeLa	human cervical cancer cells
HPLC	high performance liquid chromatography
HRIPT	human repeated insult patch test
IC_{50}	half-maximal inhibitory concentration
IgE	immunoglobulin E
IL	interleukin
kDa	kilodaltons
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LD_{50}	median lethal dose
MDA-MD-231	human breast cancer cells
MS	mass spectrometry
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCE	normochromatic erythrocytes
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
NOAEL	no-observable-adverse-effect-level
NR	not reported
OECD	Organisation for Economic Cooperation and Development
OVA	ovalbumin
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
RAST	radioallergosorbent
RIFM	Research Institute for Fragrance Materials
SDS-PAGE	sodium dodecyl sulphate-polyacrylamide gel electrophoresis
SIDS	screening information dataset
SPME	solid phase microextraction
$T_{1/2}$	elimination half life
TG	test guidelines
T_{max}	time to reach serum concentration
TNF-α	tumor necrosis factor alpha
US	United States
UV	ultraviolet
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

This is a safety assessment of the following 9 *Zingiber officinale* (ginger)-derived ingredients as used in cosmetic formulations:

Zingiber Officinale (Ginger) Extract
Zingiber Officinale (Ginger) Leaf Cell Extract
Zingiber Officinale (Ginger) Rhizome Extract
Zingiber Officinale (Ginger) Root
Zingiber Officinale (Ginger) Root Extract
Zingiber Officinale (Ginger) Root Juice
Zingiber Officinale (Ginger) Root Oil
Zingiber Officinale (Ginger) Root Powder
Zingiber Officinale (Ginger) Water

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), the majority of these ingredients are reported to function in cosmetics as skin-conditioning agents – miscellaneous (Table 1).[1] Other reported functions include antioxidants, skin protectants, antimicrobial agents, fragrance ingredients, and flavoring agents. It should be noted that skin protectant and antimicrobial functions are considered drug, not cosmetic, functions in the United States (US), and therefore, use as such does not fall under the purview of the Expert Panel for Cosmetic Ingredient Safety (Panel).

The United States (US) Food and Drug Administration (FDA) has affirmed that *Zingiber officinale* is generally recognized as safe (GRAS) as a spice, natural seasoning agent, and flavoring [21CFR182.10]. In addition, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Zingiber officinale* are considered GRAS for human consumption [21CFR182.2]. For the ingredients that are affirmed GRAS, systemic toxicity via the oral route will not be the focus of this safety assessment. Although oral exposure data are included in this report, the primary focus of this safety assessment is topical exposure and local effects.

Zingiber Officinale (Ginger) Water is reported to function only as fragrance ingredient. The Panel does not typically review ingredients that function only as fragrance ingredients, because, as fragrances, the evaluation of the safety of these ingredients is the purview of the Research Institute for Fragrance Materials (RIFM). However, according to personal communications with RIFM, it is unknown when the safety assessment of this ingredient will be prepared; therefore, it will be reviewed herein.

Zingiber officinale contains many constituents. In this assessment, the Panel is evaluating the potential toxicity of each of the *Zingiber officinale* (ginger)-derived ingredients as a whole, complex substance; toxicity from single components may not predict the potential toxicity of botanical ingredients.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Some of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website.[2] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited**.** The CAS No. used to identify the test material in the ECHA data (84696-15-1) is generic, and the ingredient that is being tested in not clearly identified; it could possibly correspond to several of the ingredients in this report, with the exception of Zingiber Officinale (Ginger) Root Oil (which has a different CAS No.). Therefore, it should be noted that when ECHA summary data are presented, it is possible that it may refer to any ginger-derived ingredient in which the CAS number 84696-15-1 is used.

Confusion exists between the distinction of ginger root versus ginger rhizome in both the *Dictionary* and published literature, and many times, it is possible that these plant names are used synonymously. Therefore, for the purposes of this report, research on the ginger rhizome juice, oil, and powder is placed under the closest root ingredient. For example, data regarding a *Zingiber officinale* (ginger) rhizome oil is placed under the name Zingiber Officinale (Ginger) Root Oil, as this name is included in the *Dictionary*. Information regarding the clarification between the root and rhizome has been requested from the Personal Care Products Council (Council).

CHEMISTRY

Definition and Plant Identification

All ingredients reviewed in this report are derived from the *Zingiber officinale* (ginger) plant. The definitions of the ginger-derived ingredients included in this review are provided in Table 1; the generic CAS number for the majority of these ingredients is 84696-15-1.[1]

Ginger is a tropical, flowering, 2 - 4 ft long perennial plant, with grass-like leaves that grow up to a foot in length.[3] The shoots and leaves grow directly from thick, underground, branched rhizomes, which have a corky, brown to golden outer skin.[4] The interior of the rhizomes are juicy, fleshy, and pale yellow in color.

Chemical Properties

According to ECHA data, a *Zingiber officinale* (ginger) extract (may refer to other ginger-derived ingredients reviewed in this report) is reported to be a liquid substance with a water solubility and log k_{ow} of 0.0004 g/l and 6.9, respectively.[2] Other chemical properties evaluated for this test substance can be found in Table 2.

Method of Manufacture

The majority of the methods below are general to the processing of these ginger ingredients. It is unknown if they apply to cosmetic ingredient manufacturing. In some cases, the definition of the ingredients, as given in the *Dictionary*, provides insight as to the method of manufacture.

Zingiber Officinale (Ginger) Extract

Air-dried Zingiber Officinale (ginger) was pulverized and percolated in 95% methanol, multiple times, until extraction completion.[5] The extracts were concentrated under reduced pressure using a rotary vapor. Concentrated extracts were kept at -20° C until use.

Zingiber Officinale (Ginger) Rhizome Extract

Ginger rhizome extracts were prepared by weighing 300 g of fresh rhizomes, and combining with a solvent (*n*-hexane or methanol) in a flask.[6] These samples were shaken for 48 h, and filtered with filter paper. The filtrate was subjected to rotary evaporation for removal of the solvent. The solvent was further removed under a purified nitrogen stream. A different *Zingiber officinale* (ginger) rhizome extract was prepared by first cleaning, peeling, chopping, and drying the rhizomes.[7] After drying, rhizomes were ground into a fine powder, and soaked in distilled water for 24 h. This aqueous extract was then filtered by double gauze and concentrated under reduced pressure.

Zingiber Officinale (Ginger) Root Extract

According to a supplier, Zingiber Officinale (Ginger) Root Extract is produced via maceration of the ginger root, followed by sterilizing filtration and evaporation.[8] Typical solvents include water, glycerin 50/50, glycerin 20/80, and refined sunflower oil. Data were also submitted from a supplier regarding the manufacturing process of a trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)).[9] This mixture is created via the grinding/milling of the plant roots, followed by aqueous extraction, solvent dilution (with hexylene glycol and caprylyl glycol), and filtration.

An aqueous ginger root extract was prepared by first peeling ginger roots.[10] Peeled ginger root (50 g) was then cut into small pieces and homogenized in 75 ml of 0.9% sodium chloride, in the presence of crushed ice. Homogenization was performed using a blender for a total of 12 min. This mixture was then filtered through cheesecloth, and the filtrate was centrifuged for 10 min. The clear supernatant was made up to 100 ml with saline.

Zingiber Officinale (Ginger) Root Juice

Fresh rhizomes of ginger (1 kg) were obtained and crushed.[11] Crushed ginger rhizomes were then squeezed in muslin cloth to obtain juice, and stored in a refrigerator until use.

Zingiber Officinale (Ginger) Root Oil

In order to create a ginger root fixed oil (non-volatile), approximately 4023 g fresh ginger were reduced to a paste using a laboratory mortar, and macerated in n-hexane, for 72 h.[12] This solution was shaken for 15 min and filtrated with filter paper. The vehicle (n-hexane) was evaporated via a rotary evaporator, leaving an oily extract. This extract was cooled and stored in a tight-capped fitted container. In order to produce a ginger root essential oil, 1000 g of fresh ginger were ground using an electric blender. The sample was placed in a conical flask and connected to a Clevenger apparatus. Distilled water was added to the flask and heated. The steam in combination with the essential oils was distilled into a graduated cylinder for 5 h, and separated from the aqueous layer. The extracted oil was kept in a refrigerator until further use.

Zingiber Officinale (Ginger) Root Powder

Fresh ginger rhizomes were washed in water to remove dirt, and chopped into small pieces.[13] Pieces were allowed to dry for 5 d. Dried samples were milled into fine particles, and sieved. The powder was stored in an air-tight container until further use. Other methods of drying include oven drying, microwave drying, and solar drying.[14]

Zingiber Officinale (Ginger) Water

According to the wINCI *Dictionary* and a supplier, Zingiber Officinale (Ginger) Water is produced by steam distillation of the roots of *Zingiber officinale*.[1,15] The distillate is then filtrated to produce the final product.

Composition and Impurities

Zingiber Officinale (Ginger) Extract

The main components of a *Zingiber officinale* (ginger) extract (solvent not stated) were determined by a solid phase microextraction (SPME) assay.[16] Identified components included camphene (7.27%), geranial (8.37%), α-zingiberene (14.50%), α-farnesene (9.14%), β-bisabolene (6.52%), and β-sesquiphellandrene (9.92%).

The total phenolic and flavonoid content of methanolic *Zingiber officinale* (ginger) leaf and stem extracts was evaluated via a 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay.[17] Two varieties of ginger in the *Zingiber officinale* family were evaluated (Halia Bentong and Halia Bara). The average phenolic content in the leaves of the Halia Bentong and Halia Bara varieties was 33.0 ± 1.13 and 39.1 ± 9.2 mg gallic acid/g dry plant material, respectively. The average flavonoid content in the leaves of the Halia Bentong and Halia Bara varieties was 5.54 ± 1.83 and 7.05 ± 7.4 mg quercetin/g dry plant material, respectively. In addition, the average phenolic content in the stems of the Halia Bentong and Halia Bara varieties was 7.8 ± 0.65 and 8.5 ± 0.81 mg gallic acid/g dry plant material, respectively. The average flavonoid content in the stems of the Halia Bentong and Halia Bara varieties was 1.36 ± 0.85 and 1.77 ± 0.75 mg quercetin/g dry plant material, respectively.

Zingiber Officinale (Ginger) Rhizome Extract

The major constituents of ginger rhizomes include carbohydrates (50-70%), lipids (3-8%), terpenes (zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, and α-curcumene), and phenolic compounds (gingerol, paradols, and shogaol).[18] Maximum phenolic content in a methanolic and hexane extract of fresh ginger rhizomes was reported to be 95.2 mg/g dry extract and 87.5 mg/g dry extract, respectively.[6]

The levels of various metals in ginger rhizome samples in four different regions of Ethiopia were evaluated via flame atomic absorption spectrometry.[19] The mean metal concentration ranges (µg/g dry weight basis) in the ginger samples were: Ca (2000 - 2540), Mg (2700 - 4090), Fe (41.8 - 89.0), Zn (38.5 - 55.2), Cu (1.1 - 4.8), Co (2.0 - 7.6), Cr (6.0 - 10.8), Mn (184 - 401), Ni (5.6 - 8.4) and Cd (0.38 - 0.97). In a different study, an aqueous *Zingiber officinale* (ginger) rhizome extract was reported to contain 5.52% gingerol and 11.7% shogaol.[20]

Zingiber Officinale (Ginger) Root Extract

According to a supplier, a trade name mixture containing Zingiber Officinale (Ginger) Root Extract (12 – 17%), is also comprised hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), Zingiber Officinale (Ginger) Root Extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%).[21] According to this supplier, this trade name mixture was free of heavy metals (< 20 ppm), chromium (< 20 ppm), lead (< 10 ppm), nickel (< 10 ppm), cobalt (< 10 ppm), antimony (< 5 ppm), arsenic (< 2 ppm), mercury (< 1 ppm), and cadmium (< 1 ppm). In addition, fragrance allergens listed in Annex III of EU Cosmetic Regulation (EC) No. 1223/2009 and pesticides were not known to be present in this trade name mixture.

The chemical composition of *Zingiber officinale* (ginger) root extract in various solvents (water at 100°C and 30°C, ethanol, methanol, acetone, 80% methanol, 80% ethanol) was evaluated.[22] Total polyphenols, flavonoids, and tannins were highest in the aqueous extract (0.84 mg/g, 2.98 g/100g, and 1.51 g/100 g, respectively). Antioxidant components and total antioxidant activity of each ginger extract can be found in Table 3. The average total amounts of protein, fat carbohydrate, vitamin C, and carotenoids from all samples were 5.09, 3.72, 38.35, 9.33, and 29 g/100g, respectively. Phosphorous, calcium, manganese, and iron were present in all samples in average amounts of 1.74, 0.88, 0.09, and 0.008 g/100g, respectively.

Zingiber Officinale (Ginger) Root Oil

A *Zingiber officinale* (ginger) oil, prepared from ginger rhizomes using hydrodistillation and extracted with pentane, was evaluated via gas chromatography (GC) and GC-mass spectrometry (MS).[23] The oil, for which the yield was 2.52%, contained 64.4% sesquiterpene hydrocarbons, 6.6% carbonyl compounds, 5.6% alcohols, 2.4% monoterpene hydrocarbons, and 1.6% esters. The main compounds were zingiberene (29.5%) and sesquiphellandrene (18.4%). Specific amounts of hydrocarbons and oxygenated constituents identified in the ginger rhizome oil are provided in Table 4.

Zingiber Officinale (Ginger) Root Powder

The compositions of *Zingiber officinale* (ginger) powders prepared by various drying methods are summarized in Table 5.[14] Polyphenol contents were similar among all samples (average amount of 12.3 mg/100 g powder). The phytochemical and mineral composition of a *Zingiber officinale* (ginger) rhizome powder was evaluated.[13] Phytins, tannins, saponins, oxalates, and glycosides were present in amounts of 0.28, 0.02, 4.01, 0.26, 0.81 mg/100g, respectively. The following minerals were present in the ginger rhizome powder: Zn (4.19 µg/g), Mn (18.9 µg/g), Cu (0.86 µg/g), Ca (34.55 µg/g), P (26.70 µg/g), Fe (1.59 µg/g), Na (38.96 µg/g), and K (36.34 µg/g).

Zingiber Officinale (Ginger) Water

According to a supplier, a trade name mixture containing Zingiber Officinale (Ginger) Water consisted of 98.5% Zingiber Officinale (Ginger) Water and phenoxyethanol (1.5%).[24]

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US FDA and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Council, of maximum reported use concentrations by product category.

According to 2021 VCRP survey data, Zingiber Officinale (Ginger) Root Extract is reported to be used in 207 formulations (131 leave-on formulations; 75 rinse-off formulations; 1 formulation diluted for bath use) and Zingiber Officinale (Ginger) Root Oil is reported to be used in 123 formulations (84 leave-on formulations; 22 rinse-off formulations; 6 formulations diluted for bath use; Table 6).[25] All other in-use ingredients are reported to be used in 4 formulations or less. The results of the concentration of use survey conducted by the Council in 2020 indicate Zingiber Officinale (Root) Extract also has the highest concentration of use in a leave-on formulation; it is used at up to 0.2% in face and neck formulations.[26] However, it should be noted that Zingiber Officinale (Ginger) Root Oil is reported to be used in "other fragrance preparations" as an essential oil, in which a few drops are used per teaspoon of carrier oil. The ingredients not in use according to the VCRP and industry survey include Zingiber Officinale (Ginger) Leaf Cell Extract, Zingiber Officinale (Ginger) Root, and Zingiber and Officinale (Ginger) Root Juice.

Incidental ingestion of these ginger-derived ingredients may occur due to use in lipstick, dentifrices, and other oral hygiene product formulations (e.g. Zingiber Officinale (Ginger) Root Extract is used at up to 0.02% in lipsticks). In addition, Zingiber Officinale (Ginger) Root Extract is reported to be used in one eye lotion formulation (concentration for this formulation type was not provided). Mucous membrane exposure may also occur as Zingiber Officinale (Ginger) Root Extract and Zingiber Officinale (Ginger) Root Oil are reported to be used in bath oils, tablets and salts, at up to 0.001%.

Additionally, some of these ginger-derived are used in cosmetic sprays and powders, and could possibly be inhaled; for example, Zingiber Officinale (Ginger) Root Extract is reported to be used in other fragrance preparations (up to 0.1%), and Zingiber Officinale (Ginger) Root Oil is reportedly used pump spray body and hand formulations (up to 0.001%), and in face powders (concentration not reported). In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles <10 μm compared with pump sprays.[27,28] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[29,30] Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[31-33]

All of the ginger-derived ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[34]

Non-Cosmetic

Zingiber officinale (ginger) has been used worldwide as a food and flavoring agent.[35] Ginger rhizomes may be consumed fresh, dried, pulverized into a spice, candied, or pickled. Ginger may also be incorporated into baked goods, or steeped in boiling water to make ginger tea. According to the US FDA (21CFR182.10), *Zingiber officinale* is GRAS as a spice, natural seasoning agent, and flavoring. In addition, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Zingiber officinale* are GRAS for human consumption (21CFR182.20), and in animal drugs, feeds, and related products (21CFR582.20).

Ginger is commonly consumed as an over-the-counter remedy for nausea and dyspepsia, and has been listed as an inactive ingredient in two orally-ingested, FDA-approved drug products.[35,36] In Asian cultures, ginger is used as a traditional medicine to treat various ailments such as arthritis, hypercholesterolemia, baldness, toothache, and respiratory conditions. Historically, ginger has been used to improve appetite, reduce nausea, and as a topical counter-irritant.

TOXICOKINETIC STUDIES

Penetration Enhancement

In Vitro

Zingiber Officinale (Ginger) Root Extract

The influence of an aqueous *Zingiber officinale* (ginger) root extract on the transdermal absorption of hydrophilic ([^{14}C]caffeine) and hydrophobic ([^{14}C]salicylic acid) penetrants was evaluated via a flow-through in vitro porcine skin system.[37] Skin samples were placed into a two-compartment diffusion cell, and the dermal side of the skin sections were perfused using the receptor fluid consisting of a buffer solution, dextrose, and bis(trimethyl)acetamide. The flow rate of the flow-through receptor solution was 4 ml/h. A 10% solution of the ginger root extract prepared in ethanol was applied to the porcine skin, with either caffeine or salicylic acid, to an area of 1 cm^2. Control samples were exposed to ethanol combined with either caffeine or salicylic acid. All doses were occluded following topical application. Receptor fluid was collected 0, 15, 30, 45, 60, 75, 90, 105, and 230 min after application, and then 3, 4, 5, 6, 7, 8, 12, 16, 20, and 24 h after application. Flux and permeability of caffeine with ginger root extract (flux: 1.67 ± 0.28 μg/cm^2/h; permeability: 0.78 ± 0.13 cm/h*10^3) was compared to the flux and permeability of caffeine with ethanol (flux: 0.58 ± 0.08 μg/cm^2/h; permeability: 0.29 ± 0.04 cm/h*10^3). No significant differences were observed in the absorption of [^{14}C]salicylic acid with the ginger root extract compared to the control.

Absorption, Distribution, Metabolism, and Excretion

Human

Oral

Zingiber Officinale (Ginger) Root Extract

The pharmacokinetics of active constituents found in a *Zingiber officinale* (ginger) root extract (6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol) were evaluated in humans.[38] Nine healthy volunteers received a 2 g oral dose of the ginger root extract.[38] Blood was drawn from participants at baseline, and at 0.25, 0.75, 1, 2, 4, 6, 10, 24, 48, and 72 h after ingestion. Plasma was separated from blood and evaluated via a liquid chromatography-mass spectrometry (LC-MS) analysis. Free 10-gingerol was detected in plasma with a peak concentration of 9.5 ± 2.2 ng/ml at 1 h, but was undetectable after 2 h post-dosing. Free 6-shogaol was detected in plasma at a peak concentration of 13.6 ± 6.9 ng/ml at 1 h, and was undetectable after 4 h post-dosing. No free 6-gingerol or 8-gingerol was detected in the plasma samples from 0 to 24 h post-dosing. In a multiple-dose assay, 23 healthy human subjects received either placebo (n = 11) or ginger root extracts (2.0 g/d; n = 12), for 24 d. Blood samples were drawn within 24 h of the last dose. No free 6-, 8-, or 10-gingerol and no 6-shogaol was detected in the plasma of all the subjects 24 h after the last dosing, suggesting that there was no accumulation of free 6-, 8-, or 10-gingerol or 6-shogaol in plasma after multiple daily dosing. Low levels of 6-gingerol glucuronide, 6-gingerol sulfate, and 10-gingerol glucuronide were observed in 4 subjects.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Zingiber Officinale (Ginger) Extract

No toxicity was observed in male Wistar rats (5/group) given a single oral dose of a *Zingiber officinale* (ginger) extract (concentrations ranging from 100 – 1000 mg/kg).[39] In a different study, Sprague-Dawley rats (5 rats/sex/group) were given a single oral dose of up to 5000 mg/kg steamed and dried ginger extract via gavage.[40] No mortalities or adverse effects were reported.

Zingiber Officinale (Ginger) Rhizome Extract

Five Syrian golden hamsters (5/sex/group) were given an ethanolic *Zingiber officinale* (ginger) rhizome extract via gavage in doses of 1000, 3000, or 5000 mg/kg bw.[41] Control hamsters were fed a mixture of distilled water and a polysorbate surfactant. No deaths were observed throughout the study. Reversible stomach irritation was noted directly after administration. No other toxic effects were observed.

Zingiber Officinale (Ginger) Root Powder

Sprague-Dawley rats (5/sex/group) were given either 5000 mg/kg bw *Zingiber officinale* (ginger) rhizome powder, or distilled water, via gavage.[42] No signs of acute toxicity were observed.

Zingiber officinale (ginger) extract (potential inference source for one or more ginger-derived ingredients)

An acute toxicity assay on a *Zingiber officinale* (ginger) extract in an olive oil vehicle was performed according to Organisation for Economic Cooperation and Development (OECD) test guidelines (TG) 423.[2] Three female Wistar rats were given a single administration of the test substance (2000 mg/kw bw ginger extract in olive oil) via drinking water. Animals were inspected daily for the next 14 d. The LD_{50} was determined to be greater than 2000 mg/kg bw.

Short-Term Toxicity Studies

Animal

Oral

Zingiber Officinale (Ginger) Rhizome Extract

Syrian golden hamsters (5/sex/group) were given an ethanolic *Zingiber officinale* (ginger) rhizome extract via gavage in doses of 1000, 3000, or 5000 mg/kg bw, for 30 d.[41] Control hamsters were fed a mixture of distilled water and a polysorbate surfactant. At the end of the treatment period, animals were sacrificed and vital organs were examined. Body weights and water and food intake were similar among control and treated groups. No abnormal histopathology was observed.

Zingiber Officinale (Ginger) Root Extract

Female Sprague-Dawley rats (6/group) were given 0.5 ml of saline or a *Zingiber officinale* (ginger) root extract (50 or 500 mg/kg), daily, via gavage, for 4 wk.[10] Mortality, hematological parameters and systemic toxicity was evaluated. No mortalities were reported throughout the study period. Total lactate dehydrogenase levels in serum was statistically significantly higher in rats treated with 500 mg/kg ginger root extract compared to controls. Histopathological examinations revealed similar results in the lungs and liver in control and treated rats.

Zingiber Officinale (Ginger) Root Oil

Male Wistar rats (10/group) were given either 0.02 or 0.002 ml/kg bw of a *Zingiber officinale* (ginger) root fixed oil, or 0.04 ml/kg bw *Zingiber officinale* (ginger) root essential oil, via gavage, for 60 d.[12] (The production of the essential and fixed oils are provided in the Method of Manufacture section of this report.) A control group received 0.5 ml/kg bw corn oil over the same time period. Behavioral, morphological, macroscopic, hematological, and histomorphological parameters were evaluated. A statistically significant ($p < 0.05$) increase in weights of the kidneys, lungs, liver, and spleen was observed in animals treated with the fixed ginger root oil, at both doses, compared to controls. A statistically significant decrease in alkaline phosphatase (ALP; $p < 0.05$) and increase in alanine transaminase was recorded in animals treated with 0.002 ml/kg bw ginger root fixed oil. Some forms of pathologies in the liver and spleen were observed in rats treated with ginger root fixed oil; however, these effects were not observed in animals treated with ginger root essential oil. No significant organ weight differences were observed in animals treated with ginger root essential oil, compared to controls. Aspartate aminotransferase (AST) values were significantly reduced in animals treated with 0.04 ml/kg bw ginger root essential oil, compared to controls. No observable differences in the histology of the heart, lung, and kidney, were observed, in either ginger-treated group, compared to the control group. Test effects were reversed after study termination.

Zingiber Officinale (Ginger) Root Powder

Sprague-Dawley rats (5/sex/group) were given either 500, 1000, or 2000 mg/kg bw *Zingiber officinale* (ginger) rhizome powder, via gavage, each day, for 28 d.[42] A control group received distilled water. Results were similar among ginger-treated and control rats regarding body weight, behavior, histopathology, and laboratory parameters. Statistically significant increased numbers of white blood cells, neutrophils, and lymphocytes were noted in all ginger-treated groups, compared to controls.

A *Zingiber officinale* (ginger) root powder (5 ml/kg) in 5% gum arabic was given to Sprague-Dawley rats (5 rats/sex/group) at doses of 500, 1000, and 2000 mg/kg bw, via gavage, for 35 d.[43] Five males and 5 females were given the vehicle (5% gum arabic), only. Mortality, behavior, growth, food and water consumption, hematological parameters, and histopathological parameters were evaluated. All parameters evaluated were similar between control and treated groups, however, a dose-related decrease in serum lactate dehydrogenase activity in males was observed. Treatment with 2000 mg/kg of the ginger powder led to slightly reduced absolute and relative weights of the testes.

Human

Oral

Zingiber Officinale (Ginger) Extract

The potential toxic effects of a steamed ethanolic *Zingiber officinale* (ginger) extract was evaluated in a 12-wk, randomized, double-blind, placebo-controlled trial.[44] Seventy healthy obese participants were given an oral dose of either steamed ginger extract (200 mg in capsule form; n = 36), or a placebo (n = 34), daily. Blood pressure, pulse, and hematological and biochemical parameters (white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet, ALP, gamma-glutamyl transferase, total bilirubin, total protein, albumin, blood urea nitrogen, creatinine, glucose, creatinine kinase, lactate dehydrogenase) were evaluated. All clinical test results were normal, and all participants completed the study. No extract-related adverse effects were observed.

Subchronic Toxicity Studies

Oral

Zingiber Officinale (Ginger) Root Oil

A 13-wk oral toxicity assay was performed in Wistar rats (5 rats/sex/group).[45] Animals were either left untreated, treated with the vehicle control (paraffin oil), or treated with 100, 250, or 500 mg/kg *Zingiber officinale* (ginger) oil. Administrations occurred via gavage once per day. Mortality, body weight, food consumption, hematological parameters, and histopathological parameters were similar in control and treated groups. The no-observed-adverse-effect level (NOAEL) was determined to be greater than 500 mg/kg/d.

Chronic Toxicity Studies

Oral

Zingiber Officinale (Ginger) Root Powder

The potential chronic toxicity of a *Zingiber officinale* (ginger) rhizome powder was evaluated in Sprague-Dawley rats (20 rats/sex/group).[42] Animals were given the powder, via gavage, in doses of either 250, 500, or 1000 mg/kg bw, for 12 mo. Control animals were given distilled water. On day 366, animals were euthanized, and histopathological and hematological parameters were evaluated. No treatment-related, serious, adverse clinical effects were noted during the 12 mo observation period. Body weights and food and water consumption were similar amongst all dose levels. The NOAEL was considered to be 1000 mg/kg bw. Hematological and biochemical parameters were generally similar among control and treated groups. However, statistically significant differences were observed in hemoglobin, white blood cell, neutrophil, lymphocyte, cholesterol, triglyceride, and glucose numbers, in rats treated with 500 and 1000 mg/kg bw ginger rhizome powder, compared to controls. Histopathological examination revealed no apparent adverse effects after ginger rhizome treatment (at any dose) compared to controls.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Zingiber Officinale (Ginger) Rhizome Extract

Reproductive effects of an aqueous *Zingiber officinale* (ginger) rhizome extract were evaluated in female ICR mice, at different dosing intervals.[7] At each dosing interval, mice were given either 250, 500, 1000, or 2000 mg/kg bw of the test article via gavage. A control group was treated with distilled water. For the main study, female mice (25/group) were dosed with the test substance for 90 d, and throughout mating and gestation. On gestation day (GD) 20, mice were killed and fetuses were evaluated. For estrous cycle evaluation, mice (10/group) were treated for 2 wk before evaluating vaginal cytology, and throughout a 20-d evaluation period (35 d total). During the evaluation period, estrous cycle phases were screened daily, and vaginal cytology was assessed. Pre-implantation effects were evaluated in 10 mice/group treated 20 d before, and throughout mating. Post-implantation effects were evaluated in mice (10/group) treated 20 d before, and throughout gestation. All pregnant females survived until necropsy, except for one female treated with 1000 mg of the extract in the pre-implantation group, and in 2 females treated with 2000 mg of the extract in the post-implantation group. High doses of the ginger rhizome extract significantly reduced the number of live fetuses, and increased fetal death and resorption, compared to controls ($p \leq 0.05$). Mice treated with 2000 mg/kg bw displayed significant decreases in implantation sites, compared to control animals ($p \leq 0.05$). At the highest dose level, estrous cycles were prolonged, with a significant decrease in the duration of the luteal phase, compared to control animals. The NOAEL was determined to be 500 mg/kg bw.

Zingiber Officinale (Ginger) Root Powder

The effect of prenatal exposure to a *Zingiber officinale* (ginger) rhizome powder on pregnancy outcome and postnatal development of Sprague Dawley rats was evaluated.[46] Pregnant rats were given dry powder extracts (500 mg/kg/d ; n = 4 or 1000 mg/kg/d; n = 5) of ginger rhizomes via gavage on GD 5-15. A negative, untreated control group consisted of 6 rats. Daily food and water intake, and total weight gain was significantly reduced in ginger-fed rats compared to controls ($p < 0.05$). Significant embryonic loss was observed in ginger-treated rats ($p < 0.05$), however, growth and physical maturation parameters of offspring (pup body weight and length) exposed to ginger were unaffected. No external congenital anomalies were found in either treated or control groups.

The effect of *Zingiber officinale* (ginger) rhizome powder (50 or 100 mg/kg/d) on spermatogenesis and sperm parameters were evaluated in male Wistar rats (10 rats/group).[47] Animals were treated orally for 20 d. The method of oral administration was not stated. A control group consisting of 10 rats received treatment with distilled water, only. Serum total testosterone levels was significantly increased in the group treated with 100 mg/kg/d ginger rhizome extract, compared to the control group ($p < 0.05$). Sperm viability and motility were significantly increased in the ginger-treated groups compared to controls ($p < 0.05$). Luteinizing hormone levels, follicle stimulating hormone levels, sperm concentration, morphology, and testes weights were similar in both ginger-treated and control groups.

ANTI-REPRODUCTIVE TOXICITY STUDIES

Treatment with *Zingiber officinale* (ginger) in rats resulted in an ameliorating effect against several reproductive toxicants.[48-52] Toxicants evaluated in these studies included aluminum chloride, ethanol, cisplatin, sodium arsenite, and cadmium chloride.

GENOTOXICITY STUDIES

In Vitro

Zingiber Officinale (Ginger) Root Oil

A *Zingiber officinale* (ginger) essential oil prepared from the rhizomes of ginger was tested for the induction of reverse mutations in *Salmonella typhimurium* strains TA1535, TA98, TA100, and TA102, with and without metabolic activation.[53] The oil was tested at concentrations of 10, 50, 100, 1000, and 3000 µg/plate. No indication of mutagenic activity was observed.

Zingiber officinale (ginger) extract (potential inference source for one or more ginger-derived ingredients)

An Ames assay was performed on a *Zingiber officinale* (ginger) extract (up to 5 µl/plate) using *S. typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102, with and without metabolic activation.[2] This assay was performed according to OECD TG 471. The test substance was considered to be non-genotoxic.

CARCINOGENICITY STUDIES

No carcinogenicity studies were found in the published literature, and unpublished data were not submitted.

ANTI-CARCINOGENICITY STUDIES

In Vitro

Zingiber Officinale (Ginger) Rhizome Extract

The anticancer activity of a *Zingiber officinale* (ginger) rhizome extract (12.5, 25, 50, 100, 200, and 400 µg/ml) against human cervical cancer (HeLa) cells and breast cancer (MDA-MD-231) cells was evaluated via a 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) and colony formation assay.[54] The rhizome extract inhibited proliferation in both cell lines in a dose- and time-dependent manner. The effect of a *Zingiber officinale* (ginger) rhizome extract (0, 10, 50, 100, 200, 500, 800, 1000, and 1500 µg/ml) on the proliferation and apoptosis of colon cancer cell lines (HCT 116 and HT 29) was also evaluated via an MTT assay.[55] The ginger extract inhibited proliferation of HCT 116 and HT 29 cells with an half-maximal inhibitory concentration (IC_{50}) of 496 ± 34.2 µg/ml and 455 ± 18.6 µg/ml, respectively. Ginger extract also caused an increase in apoptosis of the cancer cell lines in a dose-dependent manner.

Animal

Zingiber Officinale (Ginger) Extract

Potential anti-prostate cancer activity of a whole *Zingiber officinale* (ginger) extract was evaluated in male Balb/c nude mice (6 mice/group).[56] Human prostate (PC-3) xenografts were subcutaneously implanted in all test mice. Animals were fed 100 mg/kg/d ginger extract in phosphate buffered saline for 8 wk. A control group received the vehicle only. Tumors in vehicle-treated control animals showed unrestricted progression, while ginger extract treatment resulted in a time-dependent inhibition of tumor growth over the 8-wk study period. A reduction in tumor burden by 56% was observed after 8 wk of ginger extract treatment. The mean final tumor volume was significantly less in ginger extract treated mice compared to control mice ($p < 0.05$).

The effect of an ethanolic *Zingiber officinale (*ginger) extract on ethionine-induced hepatoma was evaluated in male Wistar rats (6 rats/group).[57] Rats were randomly divided into 5 groups based on diet: i) control (given normal rat chow), ii) olive oil, iii) ginger extract (100 mg/kg body weight), iv) choline-deficient diet + 0.1% ethionine to induce liver cancer (positive control) and v) choline-deficient diet + ginger extract (100mg/kg body weight). A significant reduction in positive staining of tumor necrosis factor (TNF)-α and expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) was observed in rats treated with ginger ($p < 0.05$), compared to rats in the positive control group. In addition, treatment with ginger lowered liver nodule incidence by 17%, compared to the positive control group.

OTHER RELEVANT STUDIES

Ultraviolet (UV)-Protective Effects of Ginger

Zingiber Officinale (Ginger) Rhizome Extract

The following study is included in this report as it may be helpful in addressing cosmetic safety concerns regarding phototoxicity. Male C57BL/6 mice (5 mice/group) were subjected to mid-wavelength ultraviolet light (UVB) exposure (200 mJ/cm^2) every alternate day for 2 wk, and then given different oral doses of an aqueous *Zingiber officinale* (ginger) rhizome extract (1% and 2.5%), following each UVB exposure.[20] A control group received UVB radiation followed by distilled water. The method of oral administration was not stated. Mice were killed 24 h after the last irradiation, and blood was collected. The dorsal skin was removed and measured for cytokines and hematoxylin and eosin staining. Treatment with the ginger rhizome extract reduced the effects of UVB-induced hyperplasia, infiltration of leukocytes, and dilation of blood vessels in the dermis of mice, in a dose-dependent manner. The protective effects of *Zingiber officinale* (ginger) rhizome extract, gingerol, and shogaol, were also evaluated in human epidermal keratinocyte (HaCaT) cells. HaCaT cells were UVB-irradiated (100 mJ/cm^2) and cultured with test substances. Treatment with *Zingiber officinale* (ginger) rhizome extract, gingerol, and shogaol at concentrations up to 10 µg/ml or 10 µM had an insignificant effect on the toxicity of irradiation. However, all test substances inhibited production of cytokines in UVB-irradiated HaCaT cells.

Immunomodulatory Effects

The following studies were included as they may helpful in addressing cosmetic safety concerns regarding allergenicity/ hypersensitivity of the ginger-derived ingredients evaluated in this report.

Zingiber Officinale (Ginger) Extract

Anti-inflammatory effects of a whole *Zingiber officinale* (ginger) extract were evaluated in a murine asthma model.[58] Lung inflammation was induced in C57/B16 mice, via house dust mite (HDM) sensitization (intranasally), for 10 d. Throughout this period, mice also received a ginger extract (40 mg/kg) via gavage in 2% hydroxypropyl methylcellulose and 2.5% polyethylene glycol, twice daily. Control mice received the vehicle only. Bronchoalveolar lavages (BAL) and histologic analyses were performed following study completion. In addition, lung homogenate interleukin-4 (IL-4) concentrations were evaluated. Significant lung inflammation and increases in BAL total cell counts were evaluated after HDM administration. Co-administration of ginger extracts significantly decreased BAL cell counts compared with control mice ($p < 0.05$). The ginger extract also decreased lung concentration of IL-4 ($p < 0.05$), by 59%, compared to control animals.

Zingiber Officinale (Ginger) Powder

The anti-allergic effects of *Zingiber officinale* (ginger) powder was evaluated using a mouse allergy model.[59] Female Balb/c mice (8-10/group) were sensitized via an injection of ovalbumin (OVA), twice, in a 2-wk interval. Mice were fed diets containing 2% *Zingiber officinale* (ginger) powder, or a control diet, from 2 wk before the first injection of OVA until the end of the experiment. Two wk after the second injection, sensitization was followed by intranasal challenges, daily, for 6 d, with OVA, in all groups. Mice with OVA-induced allergic rhinitis and treatment with ginger displayed a reduction in the severity of sneezing and nasal rubbing by nasal sensitization of OVA and suppressed infiltration of mast cells in nasal mucosa and secretion of OVA-specific IgE in serum, compared to control animals.

Zingiber Officinale (Ginger) Rhizome Extract

Four patients with IgE-mediated allergy to *Zingiber officinale* (ginger) were evaluated in a study to analyze specific allergens of the ginger rhizome.[60] Two patients reported previous dyspnea and gastrointestinal symptoms following ingestion of ginger. One patient reported palpitations, hyperhidrosis, and loss of consciousness after consumption of raw ginger. Another patient reported facial angioedema and conjunctival irritation after handling ginger powder, but no symptoms after ingestion of ginger. Skin prick tests with a raw ginger extract were positive in all patients. Three healthy control subjects had negative skin prick tests to raw ginger. The ginger extract showed protein bands ranging from 90 kilodaltons (kDa) to 8 kDa. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) IgE immunoblotting assays were performed using individual patient sera. IgE-reactivity bands with molecular weights of approximately 30 and 32 kDa were observed in all patient sera. Serum from one patient revealed bands of 8-10 kDa, and serum for another patient revealed a band of 8 kDa. The 8-, 10-, 30-, and 32-kDa protein bands of the raw ginger extract were excised and analyzed. The analysis of the peptides by mass spectrometry corresponded to the cysteine protease GP-1, for the 30- and 32-kDa band. No matches were found for the 8- and 10-kDa bands.

Zingiber Officinale (Ginger) Root Oil

The anti-hypersensitivity effect of a volatile oil of *Zingiber officinale* (ginger) was evaluated in female ICR mice (12/group).[61] Mice were sensitized with 0.5% dinitrofluorobenzene (DNFB) in absolute acetone and olive oil, onto shaved abdominal skin, at the beginning of the experiment. Five days after initial sensitization, animals were challenged with 10 µl DNFB on both sides of the left ears. The right ear was treated with the vehicle (acetone and olive oil). Mice were then treated with the vehicle, ginger oil (0.125, 0.25, and 0.5 g/kg bw), or dexamethasone sodium phosphate (0.005 g/kg), via gavage, daily, for 5 d. Following the 5-d test substance administration, a DNFB challenge was performed, and mice were sacrificed. Ear swelling, thymus, and spleen weights were noted. The ginger oil, at all doses, weakened the delayed type of hypersensitivity response to DNFB in sensitized mice ($p < 0.05$), in a dose-dependent manner.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details on the dermal irritation and sensitization studies summarized below can be found in Table 7 .

In vitro dermal irritation assays performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract and a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived ingredients) yielded negative results.[2,62] An acute dermal toxicity assay on steamed and dried *Zingiber officinale* (ginger) extract (0.5 ml) was performed in 6 New Zealand White rabbits.[40] No erythema or edema was observed 24 and 72 h after treatment on intact or abraded skin. Similarly, no irritation was noted in a 48-h patch test performed on 10 subjects, using a product containing 0.0995% Zingiber Officinale (Ginger) Root. [63]

A KeratinoSens™ ARE-Nrf2 luciferase assay and direct reactivity peptide assay (DPRA) performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract yielded negative results. [64,65] A DPRA performed using a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived ingredients) yielded positive results.[2] Assays performed in humans yielded negative results (human repeated insults patch tests (HRIPTs) performed using a serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract and a product containing 0.2% Zingiber Officinale (Ginger) Root Extract).[66,67]

OCULAR IRRITATION STUDIES

In Vitro

Zingiber Officinale (Ginger) Root Extract

An EpiOcular™ was performed on a trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%).[62] Two tissue inserts (corneal epithelial models) were incubated with the test material for 30 min. The test article as considered to be non-irritating.

Zingiber officinale (ginger) extract (potential inference source for one or more ginger-derived ingredients)

Potential ocular irritancy of a *Zingiber officinale* (ginger) extract was evaluated in an in vitro assay performed according to OECD TG 437.[2] Bovine corneas (3/group) were incubated with the test substance (ginger extract) for 10 minutes, and evaluated. Negative controls were incubated with a balanced salt solution, and positive controls were

incubated with dimethylformamide. The concentrations of the test agents used were not reported. Corneal opacity values were similar among the negative control and treated groups.

CLINICAL STUDIES

Case Reports

In 2013, a woman took an herbal medicine containing ginger for motion sickness and felt full-body pruritus soon after ingestion.[68] The woman reported use of this herbal medicine for 20 yr prior, with no symptoms. Several hours after ingestion, the woman lost consciousness and was taken to the emergency department. The patient was diagnosed with anaphylactic shock. A year later, the woman reported dyspnea and itchy rash following ingestion of a different herbal medication, also containing ginger. A skin prick test was performed using powdered zedoary, powdered ginger, powdered turmeric, powdered Japanese kelp, and microcrystalline cellulose, in order determine the causative agent. Reactions were apparent after zedoary, turmeric, and ginger skin pricks. The patient was diagnosed with immediate-type allergy to zedoary/turmeric/ginger-containing drugs and foods.

A 43-yr-old man reported interrupted urinary stream associated with dysuria, perineal, and flank pain, for 4 yr.[69] The patient also reported a feeling of warmness, chest heaviness, and palpitations. History analysis revealed that the patient had been consuming ginger tea (2 - 3 tsp dry ginger) each day, for 15 yr. One week after eliminating ginger from the diet, symptoms began to recede. All symptoms were completely cleared after 8 wk without ginger consumption.

Four subjects with reported occupational allergic contact dermatitis from spices were evaluated using patch testing and prick testing.[70] Eleven spices (including powdered ginger), were put on a filter paper in a test chamber, moistened with a drop of water, and placed on the back, under occlusion. Patches stayed in placed for 2 d. One patient elicited a strong (2+) reaction to the ginger powder spice. No patients displayed reactions to skin prick testing.

A 26-yr-old man employed at a spice factory reported shortness of breath and rhinitis approximately 2 yr after starting the job.[71] By the third year, the patient reported serious attacks of dyspnea with wheezing. When assigned a different job that did not require exposure to spices, all symptoms of atopic disease diminished. Total IgE, and allergen-specific IgE, radioallergosorbent (RAST) inhibition were evaluated using various powdered spices. Specific IgE antibodies against all evaluated spices were observed in patient sera. Percent IgE binding to coriander, curry, mace, paprika, ginger, white pepper, and mugwort were reported to be 45, 44, 26, 30, 27, 13, and 5%, respectively. IgE-binding components from coriander did not cross-react with the IgE-binding components from ginger and paprika.

Forty-five female spice-factory workers were recruited to evaluate possible allergenicity to various spices (chili pepper, paprika, pepper, parsley, garlic, onion, parsnip, ginger, turmeric, salt, and dextrose). Forty-five women without constant exposure to spices were also recruited as controls. Intradermal skin tests were performed with an aqueous extract of the individual spices, in exposed and control workers. Skin reactions were read after 20 min. The most frequent positive dermal reactions occurred with chili pepper (13.3%), followed by paprika and parsnip (11.1%), pepper and turmeric (6.7%), and onion and ginger (2.2%). Among control workers, only 1 of 45 reacted to individual allergens, specifically with the chili pepper extract.

Spice Allergy in Spice-Sensitive Patients

Scratch tests with powdered commercial spices were performed in 70 atopic subjects with positive skin tests to birch and/or mugwort pollens and celery.[72] Scratch tests were also performed on 12 healthy controls. Aniseed, fennel, coriander, and cumin caused the highest number of positive reactions (46, 28, 26, and 24 patients, respectively). Ginger caused a positive scratch test in 3 of 70 patients.

SUMMARY

The safety of 9 *Zingiber officinale* (ginger)-derived ingredients as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, these majority of these ingredients are reported to function in cosmetics as skin-conditioning agents – miscellaneous; additional functions were also reported. *Zingiber officinale* is GRAS in the US as a spice, natural seasoning, and flavoring agent. In addition, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of *Zingiber officinale* are considered GRAS for human and animal consumption.

According to 2021 VCRP survey data, Zingiber Officinale (Ginger) Root Extract is reported to be used in 207 cosmetic formulations (131 leave-on formulations; 75 rinse-off formulations; 1 formulation diluted for bath use). Zingiber Officinale (Ginger) Root Oil is reported to be used in 123 total formulations. All other in-use ingredients are reported to be used in 4 formulations or less. The results of the concentration of use survey conducted by the Council indicate Zingiber Officinale (Root) Extract also has the highest concentration of use in a leave-on formulation; it is used at up to 0.2% in face and neck formulations.

The influence of a *Zingiber officinale* (ginger) root extract on the transdermal absorption of [^{14}C]caffeine and [^{14}C]salicylic acid was evaluated in porcine skin. The dermal absorption of [^{14}C]caffeine was significantly higher with the ginger root extract compared to the control (ethanol). No significant differences were observed in the absorption of [^{14}C]salicylic acid with the ginger root compared to the control.

Nine healthy volunteers were given a 2 g dose of *Zingiber officinale* (ginger) root extract in order to evaluate metabolism. Plasma was evaluated at various intervals following ingestion. Metabolites found in the plasma included 10-

gingerol and 6-shogaol. In a multiple-dose assay, 23 healthy volunteers received a placebo or 2 g *Zingiber officinale* (ginger) root extract, once a day, for 24 d. No free 6-, 8-, and 10-gingerol or 6-shogaol were detected in the plasma of any the subjects 24 h after the last dosing, suggesting that there was no accumulation of free 6-, 8-, and 10-gingerol or 6-shogaol in plasma after multiple daily dosing.

No adverse effects were reported in oral toxicity assays on *Zingiber officinale* (ginger) extracts performed in rats at up to 5000 mg/kg. Similarly, no adverse effects were reported in an acute oral toxicity assay involving Sprague-Dawley rats given up to 5000 mg/kg *Zingiber officinale* (ginger) rhizome powder. Reversible stomach irritation was observed in an acute oral toxicity assay performed in Syrian golden hamsters given *Zingiber officinale* (ginger) root powder. No other toxic effects were observed.

In a short-term oral toxicity assay, Syrian golden hamsters were given an ethanolic *Zingiber officinale* (ginger) rhizome extract, via gavage, at up to 5000 mg/kg bw/d, for 30 d. No signs of toxicity were observed. Female Sprague-Dawley rats were given up to 500 mg/kg of a *Zingiber officinale* (ginger) root extract, daily, via gavage, for 4 wk. Elevated total lactate dehydrogenase levels in the serums of high-dosed animals were observed; however, no other adverse effects were reported. In a 60-d study, male Wistar rats were given either 0.02 or 0.002 ml/kg bw of a *Zingiber officinale* (ginger) root fixed oil, or 0.04 ml/kg bw *Zingiber officinale* (ginger) root essential oil, via gavage, daily. Reversible, statistically significant increases in kidney, lung, liver, and spleen weights, and pathologies in the liver and spleen, were observed in animals treated with fixed ginger essential oil. These effects were not observed in animals treated with ginger root essential oil. In a 28-d study, Sprague-Dawley rats were given up to 2000 of a *Zingiber officinale* (ginger) rhizome powder, daily, via gavage. Statistically significant increased numbers of white blood cells, neutrophils, and lymphocytes were noted in all ginger-treated groups, compared to controls. No other adverse effects were reported. In a different study, a *Zingiber officinale* (ginger) root powder was orally administered to Sprague-Dawley rats at doses of up to 2000 mg/kg bw/d, via gavage, for 35 d. All parameters evaluated were similar between control and treated groups, however, a dose-related decrease in serum lactate dehydrogenase activity in males, was observed. In a 13-wk oral toxicity assay, a *Zingiber officinale* (ginger) root oil was administered to Wistar rats, each day, via gavage, at doses up to 500 mg/kg/d. The NOAEL was determined to be greater than 500 mg/kg/d. The potential chronic toxicity of a *Zingiber officinale* (ginger) rhizome powder was evaluated in Sprague-Dawley rats. Animals were treated via gavage in doses up to 1000 mg/kg bw, for 12 mo. No treatment-related, serious, adverse clinical effects were noted during the 12 mo.

In a human assay, an ethanolic *Zingiber officinale* (ginger) extract (200 mg) was given to 36 healthy, obese participants via a capsule, each day, for 12 wk. No extract-related adverse effects were observed.

The reproductive effect of an aqueous Zingiber officinale (ginger) rhizome extract (up to 2000 mg/kg bw/d; gavage administration) was evaluated in ICR mice. Estrous cycles, pre-implantation, and post-implantation effects were evaluated. High doses of the ginger rhizome extract significantly reduced the number of live fetuses, and increased fetal death and resorption, compared to controls ($p \leq 0.05$). Mice treated with 2000 mg/kg bw displayed significant decreases in implantation sites, compared to control animals ($p \leq 0.05$). The NOAEL was determined to be 500 mg/kg bw. The effect of prenatal exposure to a *Zingiber officinale* (ginger) rhizome powder on pregnancy outcome and postnatal development of Sprague Dawley rats was evaluated. Pregnant rats were given dry powder extracts (500 mg/kg/d ; n = 4 or 1000 mg/kg/d; n = 5) of ginger rhizomes via gavage on GD 5-15. Significant embryonic loss was observed in ginger-treated rats ($p < 0.05$); however, growth and physical maturation parameters of offspring (pup body weight and length) exposed to ginger were unaffected. The effect of a *Zingiber officinale* (ginger) rhizome powder (up to 100 mg/kg/d; 20 d oral administration) on sperm parameters were evaluated in male Wistar rats. Serum total testosterone levels, sperm viability, and sperm motility were statistically increased in ginger-treated rats compared to controls ($p < 0.05$). Treatment with *Zingiber officinale* (ginger) resulted in an ameliorating affect against several reproductive toxicants (aluminum chloride, ethanol, cisplatin, sodium arsenite, and cadmium chloride) in several anti-reproductive toxicity assays.

No mutagenicity was observed in an Ames assay performed using a *Zingiber officinale* essential oil (up to 3000 µg/plate; with and without metabolic activation), on *S. typhimurium* strains TA1535, TA98, TA100, and TA102. An Ames assay was performed using a *Zingiber officinale* (ginger) extract (may refer to other ginger-derived ingredients; up to 5 µl/plate; with and without metabolic activation) on *S. typhimurium* strains TA1535, TA1537, TA98, TA100, TA102. The test substance was considered to be non-mutagenic.

The anti-cancer effect of a *Zingiber officinale* (ginger) rhizome extract (up to 400 µg/ml) on human cervical and breast cancer cells was evaluated in vitro. The rhizome extract inhibited proliferation in both cell lines in a dose- and time-dependent manner. A similar assay was performed in order to evaluate the effect of *Zingiber officinale* (ginger) rhizome extract (up to 1500 µg/ml) in colon cancer cell lines. The ginger rhizome extract inhibited proliferation and increased apoptosis in the human colon cancer cell lines, in a dose-dependent manner. In a mouse assay, the potential anti-prostate cancer effect of a whole *Zingiber officinale* (ginger) extract (100 mg/kg/d; 8-wk oral administration) was evaluated in male Balb/c nude mice with subcutaneously implanted human prostate xenografts. A reduction in tumor burden by 56% was observed after 8 wk of ginger extract treatment. The effect of an ethanolic *Zingiber officinale (*ginger) extract (100 mg/kg bw) on ethionine-induced hepatoma was evaluated in male Wistar rats. Treatment with ginger lowered liver nodule incidence by 17%, compared to the positive control group.

The potential UV-protective effects of an aqueous *Zingiber officinale* (ginger) rhizome extract (1 and 2.5%) was evaluated in male C57BL/6 mice. Treatment with the ginger rhizome extract reduced the effects of UVB-induced hyperplasia, infiltration of leukocytes, and dilation of blood vessels in the dermis of mice, in a dose-dependent manner. An

in vitro assay was also performed using UVB-irradiated HaCaT cells to evaluate the potential protective effects of *Zingiber officinale* (ginger) rhizome extract, gingerol, and shogaol. All test substances inhibited production of cytokines in UVB-irradiated HaCaT cells.

The anti-inflammatory effects of a whole *Zingiber officinale* (ginger) extract was evaluated in C57/B16 mice. Lung inflammation was induced via intranasal HDM sensitization, for 10 d. Mice also received the ginger extract (40 mg/kg/d) via gavage, twice daily. Ginger extracts resulted in a statistically significant decrease in BAL cell counts and lung concentrations of IL-4, compared to controls ($p < 0.05$).

The anti-allergic effects of a *Zingiber officinale* (ginger) powder was evaluated in female Balb/c mice. Mice were sensitized via OVA injection, and fed diets containing 2% *Zingiber officinale* (ginger) powder. Mice with OVA-induced allergic rhinitis and treatment with ginger displayed a reduction in the severity of sneezing and nasal rubbing by nasal sensitization of OVA and suppressed infiltration of mast cells in nasal mucosa and secretion of OVA-specific IgE in serum, compared to control animals.

The anti-hypersensitivity effect of a volatile oil of *Zingiber officinale* (ginger) was evaluated in female ICR mice. Mice were initially dermally sensitized with DNFB in acetone and olive oil. Treated mice were given ginger oil (up to 0.5 g/kg bw), via gavage, daily, for 5 d. Following the 5-d test substance administration, a DNFB challenge was performed, and mice were sacrificed. The ginger oil, at all doses, weakened the delayed type of hypersensitivity response to DNFB in sensitized mice ($p < 0.05$), in a dose-dependent manner.

Four patients with IgE-mediated allergy to *Zingiber officinale* (ginger) were evaluated to analyze the specific allergens of the ginger rhizomes via IgE immunoblotting assays. IgE-reactivity bands with molecular weights of approximately 30 and 32 kDa were observed in all patient sera. The analysis of the peptides by mass spectrometry corresponded to the cysteine protease GP-1, for the 30- and 32-kDa band.

In vitro dermal irritation assays performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract and a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived ingredients) yielded negative results. An acute dermal toxicity assay on steamed and dried *Zingiber officinale* (ginger) extract (0.5 ml) was performed in 6 New Zealand White rabbits. No erythema or edema was observed 24 and 72 h after treatment on intact or abraded skin. Similarly, no irritation was noted in a 48-h patch test performed on 10 subjects, using a product containing 0.0995% Zingiber Officinale (Ginger) Root. A KeratinoSens™ ARE-Nrf2 luciferase assay and direct reactivity peptide assay (DPRA) performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract yielded negative results. A DPRA performed using a *Zingiber officinale* (ginger) extract (may also infer to other ginger-derived ingredients) yielded positive results. Assays performed in humans yielded negative results (HRIPTs performed using a serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract and a product containing 0.2% Zingiber Officinale (Ginger) Root Extract).

In vitro ocular irritation assays performed on a trade name mixture containing 12-17% Zingiber Officinale (Ginger) Root Extract and a *Zingiber officinale* (ginger) extract yielded negative results.

Full-body pruritus and loss of consciousness was reported in a woman after consumption of an herbal medication containing ginger. The patient reported prior 20-yr use of this medication with no adverse effects. One yr after the initial incident, the patient reported dyspnea and an itchy rash following a different herbal preparation containing ginger. Skin prick tests confirmed allergy to zedoary, turmeric, and ginger. A 43-yr-old man reported dysuria, perineal and flank pain, for 4 yr. History analysis revealed that the patient had been ingesting ginger tea, each day, for 15 yr. The patient's symptoms resolved after eliminating ginger from the diet.

Four subjects with reported occupational allergic contact dermatitis from spices were evaluated using patch testing and prick testing. One patient elicited a strong (2+) reaction to the ginger powder spice. No patients displayed reactions to skin prick testing. A 26-yr-old spice factory-worker reported increasingly exacerbated dyspnea and wheezing 2 yr after starting the job. Total IgE, and allergen-specific IgE, RAST inhibition were evaluated using various powdered spices. Percent IgE binding to coriander, curry, mace, paprika, ginger, white pepper, and mug wort were reported to be 45, 44, 26, 30, 27, 13, and 5%, respectively. Forty-five female spice-factory workers were recruited to evaluate possible allergenicity to various spices (chili pepper, paprika, pepper, parsley, garlic, onion, parsnip, ginger, turmeric, salt, and dextrose) via intradermal skin tests. Only 2.2% of patients reported a positive reaction to ginger. In a different study, scratch tests with powdered commercial spices were performed in 70 atopic patients with positive skin tests to birch and/or mugwort pollens and celery. Ginger caused a positive scratch test in 3 of 70 patients.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. INCI names, definitions, and functions of the *Zingiber officinale* (ginger)-derived ingredients in this safety assessment[1]

Ingredient (CAS No.)	Definition	Function
Zingiber Officinale (Ginger) Extract [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Extract is the extract of the whole plant, *Zingiber officinale*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Leaf Cell Extract	Zingiber Officinale (Ginger) Leaf Cell Extract is the extract of a culture of the leaf cells of *Zingiber officinale*	Antioxidants, Skin Protectants
Zingiber Officinale (Ginger) Rhizome Extract	Zingiber Officinale (Ginger) Rhizome Extract is the extract of the rhizomes of *Zingiber officinale.*	Antimicrobial Agents
Zingiber Officinale (Ginger) Root	Zingiber Officinale (Ginger) Root is the root of *Zingiber officinale.*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Extract [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Root Extract is the extract of the roots of the ginger, *Zingiber officinale.*	Fragrance Ingredients; Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Juice [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Root Juice is the juice expressed from the roots of *Zingiber officinale.*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Oil [CAS No. 8007-08-7]	Zingiber Officinale (Ginger) Root Oil is obtained from the dried rhizomes of *Zingiber officinale.**	Flavoring Agents; Fragrance Ingredients; Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Root Powder	Zingiber Officinale (Ginger) Root Powder is the powder obtained from the dried, ground roots of *Zingiber officinale.*	Skin-Conditioning Agents – Miscellaneous
Zingiber Officinale (Ginger) Water [CAS No. 84696-15-1 (generic)]	Zingiber Officinale (Ginger) Water is an aqueous solution of the steam distillate obtained from *Zingiber officinale.*	Fragrance Ingredients

*the chemical class for Zingiber Officinale (Ginger) Root Oil in the *Dictionary* is essential oils and waters

Table 2. Physical and chemical properties of a *Zingiber officinale* (ginger) extract[2]

Property	Value
Physical Form	liquid
Density/Specific Gravity (g/cm^3 @ 20 ºC)	0.878
Vapor pressure (mmHg@ 20 ºC)	63.76
Boiling Point (ºC)	229.9
Water Solubility (g/L)	0.0004
log K_{ow}	6.9

Table 3. Antioxidant components and antioxidant activity of various ginger extracts[22]

Solvent	Total Polyphenols (mg/100 g)	Tannins mg/100 g	Flavonoids (mg/100 g)	Total antioxidant activity (µmol/g of sample)
Water (100 °C)	840	1510	2980	73,529.4
Water (30 °C)	838	1340	1371	79,400
Methanol	510	1120	685	98,822.5
Ethanol	565	980	278	91,176.25
Methanol (80%)	780	1280	404	85,294
Ethanol (80%)	800	1150	352	80,000
Acetone	325	670	249	32,056

Table 4. Hydrocarbons and oxygenated compounds in a *Zingiber officinale* (ginger) rhizome essential oil[23]

Constituent	Amount (%)	Constituent	Amount (%)
(*E*)-farnesene	0.73	pinanol	amount undermined
(*E,E*) α-farnesene	1.92	sabinene	trace
(*Z*)-β-Farnesene	amount undermined	santalene	trace
2,6-dimethylhepen-1-ol	0.01	terpinolene	0.09
2-ethyl hexanol	amount undermined	toluene	0.03
2-methyl butanal	amount undermined	*t*-muurolene	amount undermined
2-methyl-2-hepten-6-one	0.09	*t*-muurolol	0.14
2-pentanone	amount undermined	*trans*-2-octanol	trace
acetic acid	0.03	*trans*-isouegenol	0.60
acetone	0.02	vetivinene	0.57
allaromadendrene	trace*	zingiberene	29.54
bergametene	0.23	α-bisabolol	amount undermined
borneol	1.27	α-copaene	amount undermined
cadinol	amount undermined	α-cubebene	0.11
calamenene	amount undermined	α-eudesmol	0.11
camphene	0.61	*α*-eugenol	trace
camphor	0.06	α-gurjumene	0.01
cintronellal	0.14	α-himachallene	amount undermined
cintronellol	0.60	α-humulene	0.22
elemol	0.36	α-phellandrene	0.03
eremophyllene	0.09	α-pinene	0.21
eudesmol	0.36	α-terpineol	0.61
farnesene	6.46	α-ylangene	0.55
geranial	3.46	β-caryophyllene	0.35
geraniol	0.77	β-phellandrene	0.95
geranoic acid	0.24	β-pinene	0.61
geranylacetone	amount undermined	β-selinene	0.16
germacrene D	3.58	β-sesquiphellandrene	18.42
hexanal	0.02	β-sesquiphellandrol	0.34
ionone	amount undermined	γ-elemene	0.12
isovaleraldehyde	amount undermined	δ-elemene	1.14
lauric acid	amount undermined	δ-terpinene	0.01
limonen-10-ol	0.02	*ρ*-cymene	0.03
limonene	0.34	geranic acid	amount undermined
linalool	0.40	isobornyl acetate	0.03
methyl-*n*-heptylketone	0.03	citronelly acetate	0.39
methyl-*n*-undecylketone	0.09	geranyl acetate	amount undermined
Myrene	0.11	neryl acetate	1.22
n-butylaldehyde	Trace	1,8-cineole	0.41
neral	2.50	linalool oxide	amount undermined
nerolidol	0.54	caryophyllene oxide	0.18
n-heptanol-2-ol	0.02	acetyl furan	amount undermined
perillene	amount undermined	methyl pyrrole	amount undermined

*trace - < 0.01%

Table 5. Composition of *Zingiber officinale* (ginger) powders dried via different methods (mg/100g ginger powder)[14]

Ginger Powder	Shade dried	Solar dried	Oven dried	Microwave dried
Moisture	3.7±0.08	3.5±0.08	3.6±0.07	3.7±0.09
Protein	5.8±0.09	5.5±0.10	5.0±0.05	5.7±0.09
Crude Fiber	5.4±0.08	4.9±0.07	5.4±0.09	5.6±0.10
Fat	0.90±0.02	0.76±0.04	0.78±0.02	0.80±0.02
Ash	3.5±0.04	3.4±0.07	3.3±0.04	3.6±0.05
β-carotene	0.81±0.01	0.68±0.02	0.71±0.05	0.78±0.07
Ascorbic acid	3.8±0.07	2.2±0.08	2.3±0.09	3.5±0.10
Polyphenols	12.5±0.13	11.8±0.15	12.4±0.10	12.4±0.12
Calcium	69.2±1.02	65.3±1.04	64.4±1.02	67.6±1.03
Iron	1.8±0.05	1.6±0.06	1.5±0.03	1.6±0.02
Copper	0.75±0.03	0.46±0.06	0.68±0.03	0.70±0.02

Table 6. 2021 Frequency[25] and 2020 concentration[26] of use according to duration and exposure

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Zingiber Officinale (Ginger) Extract		**Zingiber Officinale (Ginger) Rhizome Extract**		**Zingiber Officinale (Ginger) Root Extract**	
Totals*	**4**	**0.000042 – 0.0009**	**1**	**NR**	**207**	**0.0000033 – 0.22**
Duration of Use						
Leave-On	*2*	*0.000042*	*1*	*NR*	131	*0.0001 – 0.2*
Rinse-Off	*2*	*0.0009*	*NR*	*NR*	75	*0.0001 – 0.22*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	1	*0.0000033 – 0.001*
Exposure Type						
Eye Area	NR	NR	NR	NR	3	NR
Incidental Ingestion	NR	NR	NR	NR	4	0.0072 – 0.02
Incidental Inhalation-Spray	NR	0.000042[a]	1[a]	NR	1; 51[a];40[b]	0.001 – 0.1; 0.009[a]
Incidental Inhalation-Powder	NR	NR	NR	NR	40[b]	0.0001 – 0.2[c]
Dermal Contact	4	NR	1	NR	141	0.0000033 – 0.22
Deodorant (underarm)	1[a]	NR	NR	NR	1[a]	NR
Hair - Non-Coloring	NR	0.000042 – 0.0009	NR	NR	62	0.0001 – 0.018
Hair-Coloring	NR	NR	NR	NR	NR	0.0016
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	11	0.0000033 – 0.02
Baby Products	NR	NR	NR	NR	NR	NR
	Zingiber Officinale (Ginger) Root Oil		**Zingiber Officinale (Ginger) Root Powder**		**Zingiber Officinale (Ginger) Water**	
Totals*	**123**	**0.000046 – 0.004; 100****	**4**	**NR**	**2**	**NR**
Duration of Use						
Leave-On	*84*	*0.000046 – 0.003; 100**	1	*NR*	NR	*NR*
Rinse Off	*33*	*0.001 – 0.004*	3	*NR*	1	*NR*
Diluted for (Bath) Use	*6*	*0.001*	NR	*NR*	1	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	2	NR	1	NR	NR	NR
Incidental Inhalation-Spray	14; 25[a]; 18[b]	0.00032 – 0.001; 100**	1[b]	NR	NR	NR
Incidental Inhalation-Powder	1; 18[b]	0.001 – 0.003[c]	1[b]	NR	NR	NR
Dermal Contact	108	0.000046; 100**	3	NR	1	NR
Deodorant (underarm)	5[a]	0.000046 – 0.0021	NR	NR	NR	NR
Hair - Non-Coloring	13	0.004	NR	NR	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	24	0.001	3	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
**Essential oil: diluted for use a few drops used per tsp of carrier oil
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – not reported

Table 7. Dermal irritation and sensitization studies

Ingredient	Test Article	Dose/Concentration	Test Population	Procedure	Results	Reference
IRRITATION						
In Vitro						
Zingiber Officinale (Ginger) Root Extract	Trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)	100	3 tissue inserts	EpiDermTM assay; reconstructed human epidermis; tissue inserts incubated for 60 min	Non-irritating	[62]
Zingiber Officinale (Ginger) Extract*	*Zingiber officinale* (ginger) extract*	NR	3 tissue inserts	OECD TG 439; reconstructed human epidermis	Non-irritating	[2]
Animal						
Zingiber Officinale (Ginger) Extract	*Zingiber officinale* (ginger) extract (dried)	0.5 ml; concentration not reported	6 New Zealand white rabbits	The test substance was applied to intact and abraded skin (level of occlusion not reported), and kept in place for 24 h	Non-irritating; PII = 0	[40]
Human						
Zingiber Officinale (Ginger) Root Extract	Product containing 0.0995% Zingiber Officinale (Ginger) Root Extract	0.02 ml; 100%	10 subjects	48-h application; occlusive conditions; evaluations made 30 min after patch removal	Non-irritating	[63]
SENSITIZATION						
In Vitro						
Zingiber Officinale (Ginger) Root Extract	Trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)	0.00098 - 2 mM	HaCaT cells	KeratinoSens™ ARE-Nrf2 luciferase test; OECD TG 442D	Non-sensitizing; IC_{50} > 1000 µm	[64]
Zingiber Officinale (Ginger) Root Extract	Trade name mixture comprised of Zingiber Officinale (Ginger) Root Extract (12-17%), hexylene glycol (28 -32%), caprylyl glycol (12-17%), wasabia japonica root extract (12-17%), allium sativum (garlic) bulb extract (12-17%), and water (8-12%)	100 mM	cysteine- and lysine-containing peptides (3 replicates)	DPRA; OECD TG 442C	Non-sensitizing; mean percent depletion of 1.89% (minimal reactivity)	[65]
Zingiber Officinale (Ginger) Extract*	*Zingiber officinale* (ginger) extract*	100%	cysteine- and lysine-containing peptides (3 replicates)	DPRA; OECD TG 442C	Sensitizing; mean percent depletion pf 27.81% (moderate reactivity)	[2]
Human						
Zingiber Officinale (Ginger) Root Extract	Serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract	100%; dose and application area not reported	104 subjects	HRIPT; occlusive conditions	Non-irritating and Non-sensitizing	[66]
Zingiber Officinale (Ginger) Root Extract	Product containing 2% Zingiber Officinale (Ginger) Root Extract	100%; 2 cm x 2 cm application area	53 subjects	HRIPT; semi-occlusive conditions	Non-irritating and Non-sensitizing	[67]

*potential inference source for one or more ginger-derived ingredients

DPRA = direct peptide reactivity assay; HaCaT = immortalized human keratinocytes; HRIPT = human repeat insult patch test; IC_{50} = half-maximal inhibitory concentration; OECD TG = Organisation for Economic Cooperation and Development test guidelines; PII = primary irritation index

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66. Anonymous. 2015. Repeated insult patch test (RIPT)-Shelanski method (serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract. Unpublished data submitted by Personal Care Products Council on May 11, 2021.

67. Anonymous. 2018. Repeated insult patch test (product contains 0.2% Zingiber Officinale (Ginger) Root Extract. Unpublished data submitted by Personal Care Products Council on May 11, 2021.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: May 11, 2021

SUBJECT: Zingiber Officinale (Ginger) Root Extract

Anonymous. 2015. Repeated insult patch test (RIPT)-Shelanski method (serum containing 0.19691% Zingiber Officinale (Ginger) Root Extract).

Anonymous. 2012. Study of acute skin compatibility of a test item: 48 hours occlusive patch test (product contains 0.0995% Zingiber Officinale (Ginger) Root Extract).

Anonymous. 2018. Repeated insult patch test (product contains 0.2% Zingiber Officinale (Ginger) Root Extract).

[redacted]

Report Status:	Final Report
Report Date:	October 28, 2015
[redacted]	[redacted]
[redacted]	[redacted]
Study Dates:	September 16, 2015 - October 23, 2015
Study Title:	Repeated Insult Patch Test (RIPT) –Shelanski Method
Test Material:	[redacted] serum contains 0.19691% Zingiber Officinale (Ginger) Root Extract
Sponsor:	[redacted]
Sponsor Representative:	[redacted]
Investigator:	[redacted] M.D. Dermatologist

APPROVAL SIGNATURES:

[redacted]

[redacted] uote

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: [redacted]

Start Date: September 16, 2015

Completion Date: October 23, 2015

The clinical study listed above was conducted in accordance with [redacted] Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted.

[redacted]

FINAL REPORT

Repeated Insult Patch Test (RIPT) - Shelanski Method

1.0 OBJECTIVE

The objective of this study was to determine the dermal irritation and sensitization potential of a test material.

2.0 INVESTIGATOR/INVESTIGATIVE SITE

[redacted] M.D.
Dermatologist

[redacted]

3.0 SPONSOR REPRESENTATIVE/SPONSOR

[redacted]

[redacted]

4.0 TEST MATERIAL

The following test material was provided by [redacted] and was received by [redacted] on September 15, 2015.

Test Material	Test Condition	Patch Type
[redacted]	Neat/Shake Well	Occlusive*

The test material was coded with the following [redacted] identification number:

[redacted]

5.0 STUDY DATES

This study was initiated on September 16, 2015 and was completed on October 23, 2015.

* Occlusive Strip with Flexcon® (Strukmyer LLC, Mesquite,TX or equivalent)

6.0 PANEL SELECTION

Each subject was assigned a permanent [redacted] identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by [redacted] prior to the study (Subject Demographics - Appendix I). Subjects who met the following Inclusion Criteria and none of the Exclusion Criteria were impaneled:

6.1. INCLUSION CRITERIA

a. Subject is male or female between the ages of 18 and 70 years;

b. Subject does not exhibit any skin diseases which might be confused with a skin reaction from the test material;

c. Subject agrees to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;

d. Subject agrees to refrain from getting patches wet during the course of the study;

e. Subject has signed an Informed Consent in conformance with 21CFR Part 50: "Protection of Human Subjects;"

f. Subject has completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;

g. Subject is in generally good health and has a current Subject Profile/Medical History on file;

h. Subject is dependable and able to follow directions as outlined in the protocol.

6.2. EXCLUSION CRITERIA

a. Subject is pregnant, nursing, or planning to become pregnant;

b. Subject is currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;

c. Subject reports allergies to cosmetics, toiletries, or personal care products;

d. Subject exhibits any skin disorders, sunburn, scars, excessive tattoos, etc. in the test area;

e. Subject has scheduled, or is planning to undergo, any medical or surgical procedures during the 6 week course of the study.

7.0 TEST METHOD SUMMARY

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a [redacted] technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scoring Scale

0	No visible skin reaction
±	Barely perceptible erythema
1+	Mild erythema
2+	Well defined erythema
3+	Severe erythema and edema
4+	Erythema and edema with vesiculation

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject may not have been patched again during the Induction Phase but may have been challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.

8.0 RESULTS

This study was initiated with 113 subjects. Nine subjects discontinued study participation for reasons unrelated to the test material. A total of 104 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

9.0 ADVERSE EVENTS

No adverse events were reported during the study.

10.0 CONCLUSION

Based on the test population of 104 subjects and under the conditions of this study, the test material identified as [redacted] did not demonstrate a potential for eliciting dermal irritation or sensitization.

11.0 RETENTION

Test materials and all original forms of this study will be retained by [redacted] as specified in [redacted] Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.

TABLE I

Summary of Dermal Scores

Test Material:	[redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	Discontinued								
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	Discontinued											
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	Discontinued				
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	[redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	Discontinued							
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	[redacted]

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
51	0	0	0	0	0	0	0	0	0	±	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	Discontinued										
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	0	0	0	0	Discontinued		
62	0	0	0	0	0	0	0	0	0	0	0	0
63	0	0	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	Discontinued									

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	[redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
76	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	±*
80	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	Discontinued							
82	0	0	0	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0
92	Discontinued											
93	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0

*No reaction was observed at the 96 hour evaluation.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	[redacted]

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
101	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0
108	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0
110	0	0	0	0	0	0	0	0	0	0	0	0
111	0	0	0	0	0	0	0	0	0	0	0	0
112	0	0	0	0	0	0	0	0	0	0	0	X*
113	0	0	0	0	0	0	0	0	0	0	0	0

X = Subject Absent
*No reaction was observed at the 96 hour evaluation.

Appendix I

Subject Demographics

Subject Number	Subject Initials	Age	Sex
1	AM	52	M
2	CV	52	F
3	SR	32	F
4	DT	50	F
5	KT	65	F
6	PC	70	F
7	LB	49	F
8	MF	49	F
9	BB	52	F
10	MM	50	F
11	VH	60	F
12	SP	19	M
13	JG	44	F
14	CN	44	F
15	MP	55	F
16	CM	58	F
17	MO	47	F
18	SR	61	F
19	AI	20	F
20	DS	51	F
21	KG	56	M
22	VB	54	F
23	IK	58	F
24	JW	56	F
25	DG	62	F
26	LC	67	F
27	RA	44	F
28	KG	34	F

Subject Number	Subject Initials	Age	Sex
29	NJ	33	F
30	WT	35	F
31	ST	21	F
32	DL	38	F
33	AF	62	F
34	LR	46	M
35	WH	57	F
36	LK	52	F
37	AM	18	F
38	CC	68	F
39	LC	62	F
40	YH	44	F
41	JB	53	M
42	SH	59	F
43	RB	55	M
44	LS	60	F
45	BS	61	F
46	TW	40	F
47	MR	67	F
48	MC	38	F
49	KK	34	F
50	JT	26	M
51	JM	20	M
52	GR	65	F
53	DC	48	F
54	RT	68	M
55	ML	70	F
56	TB	45	M

[redacted]uote

Appendix I

Subject Demographics (Continued)

Subject Number	Subject Initials	Age	Sex
57	AB	25	M
58	AT	35	F
59	TG	44	F
60	LD	30	F
61	KM	55	F
62	RP	65	M
63	JP	65	F
64	LH	55	M
65	TH	53	F
66	TR	21	F
67	RP	29	F
68	MF	60	F
69	KL	38	F
70	WN	23	M
71	GM	57	F
72	LB	41	F
73	BA	35	F
74	MC	38	F
75	RS	37	F
76	HS	36	F
77	AS	66	F
78	NK	54	F
79	KM	48	F
80	AM	38	F
81	PG	59	F
82	SA	47	F
83	AS	34	F
84	DL	45	F
85	BP	55	F
86	FH	50	F
87	DD	56	F
88	YG	27	F
89	MV	67	F
90	AP	48	F
91	LL	57	M
92	KS	45	F
93	KJ	58	F
94	EH	55	F
95	CG	66	F
96	DB	57	F
97	CB	44	M
98	SH	40	F
99	TB	57	F
100	PW	30	F
101	CM	38	M
102	CR	62	F
103	RC	70	M
104	CW	50	F
105	JG	30	F
106	LH	55	F
107	BB	21	F
108	MP	56	F
109	GH	59	F
110	ND	54	F
111	DW	54	F
112	TS	49	F
113	SE	29	F

[redacted]

Test item
WILD ROSE & VITAMIN C OVERNIGHT REPAIR TREATMENT - REF : [redacted]

contains 0.0995% Zingiber Officinale (Ginger) Root Extract

Study of acute skin compatibility of a test item: 48 hours occlusive patch-test

(Clinical report on 10 adult volunteers)

- Study code : 1.01_48H
- Product code : [redacted]
- Report date : 27/07/2012

[redacted]

[redacted]

[redacted]

1. Objective of Study

Assess on 10 volunteers the irritant potential of the studied test item after its unique application, maintained for 48 hours in contact with the skin, with the help of an occlusive patch.

2. Studied test item

WILD ROSE & VITAMIN C OVERNIGHT REPAIR TREATMENT - REF : [redacted]
Code ID-[redacted]

Batch number	**1205121**
Test item type	**Finished cosmetic product**
Expiry date*	**01/06/2013**
Storage conditions	**Room temperature**

* If the expiry date was not precisely provided by the Promoter (> X months), this one will be arbitrarily defined by us as the day corresponding to X months as from the date of manufacture.

3. Application conditions

Single application of 0.02 ml of the studied test item pure, on the external face of the arm, maintained for 48 hours in contact with the skin, with the help of an occlusive patch (Finn Chambers).

4. Place and dates of the study

Place: [redacted]	1st study From : 16/07/2012 To : 18/07/2012

5. Volunteers' characteristics

10 volunteers of the female or male sex from 18 to 65 years of age, with a normal skin, without any dermatological lesion on the experimental area, should be included in the study.

6. Assessment methods

The clinical quotation is made 30 minutes after the patch removal and takes in account the erythema, the papules, the vesicles and the blisters. According to their intensity, the quotation is spread out from 0 to 3. The total sum of the scores, divided by the number of volunteers, defines the mean irritation index (M.I.I.), which allows to classify arbitrarily the test item into "non irritant, slightly irritant, moderately irritant, very irritant and severely irritant".

M.I.I. ≤ 0.20	**Non irritant**
0.20 < M.I.I. ≤ 0.50	**Slightly irritant**
0.50 < M.I.I. ≤ 2	**Moderately irritant**
2 < M.I.I. ≤ 3	**Very irritant**

7. **Results** (in the table hereafter)

- ✓ 11 volunteers have been included and 10 were analyzed. (File 12719)
- ✓ The mean irritation index of the test item is 0.

8. Protocol deviations

No deviation to the protocol has been observed during this study.

9. Conclusion

The test item WILD ROSE & VITAMIN C OVERNIGHT REPAIR TREATMENT - REF : [redacted], applied pure, can be considered as **non irritant** after an application with the help of an occlusive patch (Finn Chambers) for 48 consecutive hours on 10 volunteers.
This result is conform to that obtained for the test item of same class in accordance with our database.

10. Signatures

I have re-read this report and hereby certify that the data herein correspond to the true results obtained,
[redacted] Dermatologist, Investigator.

Date: 30 JUIL. 2012 Signature: [redacted]

This report was audited by [redacted]'s Quality Control Group. It is considered to accurately reflect the generated data and current experimental protocols used complying with sound clinical practices.
Quality Department

Date: 01 AOUT 2012 Signature: [redacted]

Study # [redacted] From **16/07/2012** To **18/07/2012**

Product [redacted]

WILD ROSE & VITAMIN C OVERNIGHT REPAIR TREATMENT - REF : [redacted]

Characteristics of volunteers					Skin reactions					
Include	Initials	Sex	Age	Treatment	In-situ reaction of product	Individual scores of product	In-situ reaction on test-site 1	In-situ reaction on test-site 2	Remark	Analysed
1	GA-SA	F	29	-	-	0,00	-	-	Withdrawal	N
2	BR-MA	F	42	-	-	0,00	-	-		O
3	BR-CY	F	28	-	-	0,00	-	-		O
4	GR-CA	F	56	-	-	0,00	-	-		O
5	DE-MA	F	30	-	-	0,00	-	-		O
6	LI-BÉ	F	28	-	-	0,00	-	-		O
7	LE-DA	M	40	-	-	0,00	-	-		O
8	FR-PI	M	62	-	-	0,00	-	-		O
9	BO-RE	M	31	-	-	0,00	-	-		O
10	BO-MA	F	22	-	-	0,00	-	-		O
11	DU-VA	M	23	-	-	0,00	-	-		O

Volunteers : 11 Volunteers analysed : 10

Result (Sum of the individual scores / Nb analysed vol) **0**

Result **non irritant**

Abbreviations

E = Erythema
O = Oedema
P = Papulae
V = Vesicles
B = Blisters

Quotations

0 = no erythema
0,5 = hardly perceptible erithema
1 = slight erythema with or without d'oedema
2 = moderate erythema, oedema with or without papules
3 = significant erythema, oedema with or without papules, vesicles or blisters

[redacted]

Annex

[redacted]

REPEATED INSULT PATCH STUDY

[redacted]

CONDUCTED FOR:

[redacted]

DATE OF ISSUE:

December 18, 2018

[redacted] [redacted]

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APPENDICES

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and [redacted]s Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

[redacted]

[redacted], MD
Dermatologist
Principal Investigator

December 18, 2018
Date

[redacted]

[redacted]
Director, Dermatologic Safety Operations

December 18, 2018
Date

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

TITLE OF STUDY

Repeated Insult Patch Study

SPONSOR

[redacted]

STUDY MATERIAL

Detox Drops, F# [redacted]

DATE STUDY INITIATED

October 1, 2018

DATE STUDY COMPLETED

November 15, 2018

DATE OF ISSUE

December 18, 2018

INVESTIGATIVE PERSONNEL

[redacted], MD - Dermatologist
Principal Investigator

[redacted]
Director, Dermatologic Safety Operations

CLINICAL SITE

[redacted]

SUMMARY

One (1) product, F# [redacted], was evaluated as supplied to determine its ability to sensitize the skin of volunteer subjects with normal skin using a semi-occlusive repeated insult patch study. Fifty-three (53) subjects completed the study.

Under the conditions employed in this study, there was no evidence of sensitization to product, F# [redacted].

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of [redacted]. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 50 completed subjects. In the absence of any sensitization reactions in this sample size (50 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 3.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females, 18 years of age or older, in general good health;
2. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events (AEs);
3. Were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. Had completed a medical screening procedure; and
5. Had read, understood, and signed an informed consent (IC) agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. Had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. Had psoriasis and/or active atopic dermatitis/eczema;
4. Were females who were pregnant, planning to become pregnant during the study, or breast-feeding; and/or
5. Had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated.

3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. Patches were applied on Mondays, Wednesdays, and Fridays for 3 consecutive weeks. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2] Following the 9th evaluation, the subjects were dismissed for a Rest Period of approximately 10-15 days.

Subjects who were absent once during the Induction Phase received a make-up (MU) patch at the last Induction Visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading). Subjects who missed the 9th evaluation (N9G) but have had 9 patch applications were considered to have completed the Induction Phase.

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Following a negative Induction, a 48/72-hour sequence of "-/+," "?/+," or "+/+" resulted in an additional reading being performed at the 96-hour interval. Rechallenge was performed whenever there was evidence of possible sensitization.

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during Induction, and a single application and 2 readings at Challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK 1

DAY ACTIVITIES

1[3] Staff obtained informed consent, reviewed completed medical screening form, applied patches

2 Subject removed patches

3 Staff graded sites, applied patches

4 Subject removed patches

5 Staff graded sites, applied patches

6 Subject removed patches

WEEK 2

1 Staff graded sites, applied patches

2-6 Same as Week 1

WEEK 3

1-6 Same as Week 2

WEEK 4

1 Staff graded sites; applied make-up (MU) induction patches, if required

2 Subject removed MU induction patches

3 Staff graded MU induction sites at MU visit

2-7 Rest Period

WEEK 5

1-7 Rest Period

WEEK 6

1 Staff applied patches

2 Subject removed patches

3 Staff graded sites

4 Staff graded sites

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

[3] Study flow starting with Week 1, Day 1, will be altered when enrollment occurs other than on Monday. Study flow could be altered when a holiday occurs during the study.

- = No reaction

? = Minimal or doubtful response, slightly different from surrounding normal skin

+ = Definite erythema, no edema

++ = Definite erythema, definite edema

+++ = Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E = Marked/severe erythema

S = Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)

p = Papular response > 50%

pv = Papulovesicular response > 50%

D = Damage to epidermis: oozing, crusting and/or superficial erosions

I = Itching

X = Subject absent

PD = Patch dislodged

NA = Not applied

NP = Not patched (due to reaction achieved)

N9G = No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting [redacted]'s strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

Identification : Detox Drops, F# [redacted]
Amount Applied : 0.2mL
Special Instructions : The study material was evaporated for 15 minutes prior to patch application.

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by [redacted]. On the basis of information provided by the Sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material is kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the Sponsor and the disposition documented in the logbook.

4.3 APPLICATION OF STUDY MATERIAL

All study material was supplied by the Sponsor. Material was applied in an amount proportionate to the patch type or as requested by the Sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm. Unless otherwise directed by the Sponsor, the study material was discarded upon completion of the study.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch is secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pad is affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the Challenge Phase of a Repeated Insult Patch Test (RIPT) than that seen during Induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the Challenge Phase is generally similar to that seen during Induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. [redacted]'s preferred Rechallenge procedure involves the application of the product to naive sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a [redacted] facility in a secured room accessible only to [redacted] employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the Sponsor's review on the premises of [redacted].

7.0 RESULTS AND DISCUSSION

Sixty (60) subjects between the ages of 21 and 70 were enrolled and 53 completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II). The following table summarizes subject enrollment and disposition:

Number enrolled:		60
Number discontinued:		7
Lost to follow-up:	7	
Number completed:		53

Source: Table 1, Appendix I

There were no adverse events (AEs) reported during this study.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to product, F# [redacted]

9.0 REFERENCES

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Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980: 41-53.

Griffith JF. Predictive and diagnostic testing for contact sensitization. Toxicol Appl Pharmacol, Suppl 1969; 3:90.

Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

[redacted]

APPENDIX I

SUMMARY TABLES

[redacted]

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	60
Subjects completed induction phase	54 (90.0)
Subjects completed all phases	53 (88.3)
Total subjects discontinued	7 (11.7)
Lost to follow-up	7 (11.7)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	10 (16.7)
N (%) 45 to 65	44 (73.3)
N (%) 66 and up	6 (10.0)
Mean (SD)	53.0 (10.8)
Median	52.7
Range	21.1 to 70.4
Sex	
N (%) Male	12 (20.0)
N (%) Female	48 (80.0)
Race	
Black	39 (65.0)
Caucasian	21 (35.0)
Ethnicity	
Hispanic/Latino	8 (13.3)
Not Hispanic/Not Latino	52 (86.7)

See data listing 2 for further detail.

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Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = F# [redacted]

	Induction Reading										Challenge Phase		
Response	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Make Up**	**48hr**	**72hr**	**96hr(*)**
-	57	55	53	55	54	52	52	52	51	8	53	53	
?	0	0	1	1	1	1	1	2	1	0	0	0	
+	0	0	0	0	0	0	0	0	1	0	0	0	
Total evaluable	57	55	54	56	55	53	53	54	53	8	53	53	
Number absent	1	2	3	1	1	2	2	0	1		0	0	
Number discontinued	2	3	3	3	4	5	5	6	6		7	7	
Patch not applied	0	0	0	0	0	0	0	0	0		0	0	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N= 54)

Response	**n(%) Subjects**
-	52 (96.3%)
?	1 (1.9%)
+	1 (1.9%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

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[redacted] Study No. DS109518

Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

APPENDIX II

DATA LISTINGS

[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
002	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
003	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
004	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
005	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
006	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
007	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
008	10/01/18	10/01/18	--	10/08/18	I1	L	8
009	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
010	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
011	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
012	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
013	10/01/18	10/01/18	--	10/15/18	I4	L	15
014	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
015	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
016	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
017	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
018	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
019	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
020	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
021	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
022	10/01/18	10/01/18	--	10/05/18	I0	L	5
023	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
024	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
025	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
026	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
027	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
028	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
029	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
030	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
031	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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[redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
033	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
034	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
035	10/01/18	10/01/18	--	11/05/18	I9	L	36
036	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
037	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
038	10/01/18	10/01/18	--	10/15/18	I5	L	15
039	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
040	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
041	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
042	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
043	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
044	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
045	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
046	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
047	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
048	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
049	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
050	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
051	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
052	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
053	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
054	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
055	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
056	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
057	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
058	10/01/18	10/01/18	--	10/05/18	I0	L	5
059	10/01/18	10/01/18	11/05/18	11/08/18	C	C	39
060	10/01/18	10/01/18	--	10/19/18	I7	L	19

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
001	68.6	Female	Not Hispanic/Not Latino	Caucasian
002	66.2	Male	Not Hispanic/Not Latino	Black
003	51.6	Female	Not Hispanic/Not Latino	Black
004	62.0	Female	Not Hispanic/Not Latino	Black
005	65.8	Male	Not Hispanic/Not Latino	Black
006	51.3	Female	Not Hispanic/Not Latino	Black
007	60.6	Female	Not Hispanic/Not Latino	Caucasian
008	51.8	Female	Not Hispanic/Not Latino	Black
009	58.8	Female	Hispanic/Latino	Caucasian
010	46.5	Female	Not Hispanic/Not Latino	Black
011	59.6	Female	Not Hispanic/Not Latino	Black
012	51.5	Male	Not Hispanic/Not Latino	Black
013	26.4	Female	Not Hispanic/Not Latino	Black
014	21.1	Female	Not Hispanic/Not Latino	Caucasian
015	49.7	Female	Not Hispanic/Not Latino	Black
016	51.9	Female	Not Hispanic/Not Latino	Caucasian
017	38.0	Female	Not Hispanic/Not Latino	Caucasian
018	67.9	Female	Hispanic/Latino	Black
019	47.7	Female	Hispanic/Latino	Black
020	58.1	Male	Not Hispanic/Not Latino	Black
021	46.4	Female	Not Hispanic/Not Latino	Black
022	50.9	Female	Not Hispanic/Not Latino	Black
023	70.4	Female	Not Hispanic/Not Latino	Caucasian
024	51.8	Female	Not Hispanic/Not Latino	Caucasian
025	35.6	Female	Hispanic/Latino	Caucasian
026	59.5	Female	Not Hispanic/Not Latino	Caucasian
027	59.8	Female	Not Hispanic/Not Latino	Black
028	57.3	Female	Not Hispanic/Not Latino	Black
029	23.3	Female	Hispanic/Latino	Caucasian
030	54.7	Female	Not Hispanic/Not Latino	Black
031	59.9	Female	Not Hispanic/Not Latino	Black
032	46.6	Female	Not Hispanic/Not Latino	Caucasian
033	47.1	Male	Hispanic/Latino	Caucasian
034	63.9	Female	Not Hispanic/Not Latino	Caucasian
035	42.4	Female	Hispanic/Latino	Black
036	38.1	Female	Not Hispanic/Not Latino	Black
037	69.1	Female	Not Hispanic/Not Latino	Black

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[redacted]

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
038	54.2	Female	Not Hispanic/Not Latino	Black
039	61.2	Female	Not Hispanic/Not Latino	Black
040	54.4	Female	Not Hispanic/Not Latino	Black
041	53.2	Female	Not Hispanic/Not Latino	Black
042	46.1	Male	Not Hispanic/Not Latino	Black
043	50.8	Female	Not Hispanic/Not Latino	Caucasian
044	52.1	Female	Not Hispanic/Not Latino	Black
045	54.4	Female	Not Hispanic/Not Latino	Caucasian
046	53.6	Female	Not Hispanic/Not Latino	Caucasian
047	40.5	Male	Not Hispanic/Not Latino	Caucasian
048	64.7	Male	Not Hispanic/Not Latino	Black
049	68.7	Female	Not Hispanic/Not Latino	Black
050	55.3	Female	Not Hispanic/Not Latino	Black
051	62.7	Female	Not Hispanic/Not Latino	Caucasian
052	51.7	Male	Not Hispanic/Not Latino	Caucasian
053	52.2	Male	Not Hispanic/Not Latino	Black
054	64.5	Male	Not Hispanic/Not Latino	Black
055	43.8	Female	Hispanic/Latino	Caucasian
056	61.2	Female	Not Hispanic/Not Latino	Black
057	40.4	Female	Not Hispanic/Not Latino	Black
058	60.4	Female	Not Hispanic/Not Latino	Black
059	50.1	Male	Not Hispanic/Not Latino	Black
060	51.5	Female	Not Hispanic/Not Latino	Black

Generated on 11/26/18:14:55 by DEMOLIST.SAS / Uses: DEMOGS

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F# [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
001	-	-	-	-	-	-	X	-	-	-	-	-	
002	-	-	-	-	-	-	-	-	-		-	-	
003	-	-	-	-	-	-	-	-	-		-	-	
004	-	-	-	-	-	-	-	-	-		-	-	
005	-	-	-	X	-	-	-	-	-	-	-	-	
006	-	-	-	-	-	X	-	-	-	-	-	-	
007	-	-	?	?	?	?	?	?	?		-	-	
008	-	X	X	X	X	X	X	X	X		X	X	
009	-	-	-	-	-	-	-	-	N9G		-	-	
010	-	-	-	-	-	-	-	-	-		-	-	
011	-	-	-	-	-	-	-	-	-		-	-	
012	-	-	-	-	-	-	-	-	-		-	-	
013	-	-	-	-	X	X	X	X	X		X	X	
014	-	-	-	-	-	-	-	-	-		-	-	
015	-	-	-	-	-	-	-	-	-		-	-	
016	-	-	-	-	-	-	-	-	-		-	-	
017	-	-	X	-	-	-	-	-	-	-	-	-	
018	-	-	-	-	-	-	-	-	-		-	-	
019	-	-	-	-	-	-	-	?	+		-	-	
020	-	-	-	-	-	-	-	-	-		-	-	
021	-	-	-	-	-	-	-	-	-		-	-	
022	X	X	X	X	X	X	X	X	X		X	X	
023	-	-	-	-	-	-	-	-	-		-	-	

See Table 3.1 for Key to Symbols and Scores

MU = Make-up reading for missed induction visit

(*) When required
Generated on 11/26/18:14:55 by DETAIL.SAS/USES: RESPONSE, PRODLIST

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F# [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	-	-	-		-	-	
025	-	-	-	-	-	-	-	-	-		-	-	
026	-	-	-	-	-	-	-	-	-		-	-	
027	-	-	-	-	-	-	-	-	-		-	-	
028	-	-	-	-	-	-	-	-	-		-	-	
029	-	-	-	-	-	-	-	-	-		-	-	
030	-	X	-	-	-	-	-	-	-	-	-	-	
031	-	-	-	-	-	-	-	-	-		-	-	
032	-	-	-	-	-	-	-	-	-		-	-	
033	-	-	-	-	-	-	X	-	-	N9G	-	-	
034	-	-	-	-	-	-	-	-	-		-	-	
035	-	-	-	-	-	-	-	-	-		X	X	
036	-	-	-	-	X	-	-	-	-	-	-	-	
037	-	-	-	-	-	-	-	-	-		-	-	
038	-	-	X	-	-	X	X	X	X		X	X	
039	-	-	-	-	-	-	-	-	-		-	-	
040	-	-	-	-	-	-	-	-	-		-	-	
041	-	-	-	-	-	-	-	-	-		-	-	
042	-	-	-	-	-	-	-	-	-		-	-	
043	-	-	-	-	-	-	-	-	-		-	-	
044	-	-	-	-	-	-	-	-	-		-	-	
045	-	-	-	-	-	-	-	-	-		-	-	
046	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 11/26/18:14:55 by DETAIL.SAS/USES: RESPONSE, PRODLIST

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = F# [redacted]

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	-	-	-	-	-	-	-	-	-		-	-	
048	-	-	-	-	-	-	-	-	-		-	-	
049	-	-	-	-	-	-	-	-	-		-	-	
050	-	-	X	-	-	-	-	-	-	N9G	-	-	
051	-	-	-	-	-	-	-	-	-		-	-	
052	-	-	-	-	-	-	-	-	-		-	-	
053	-	-	-	-	-	-	-	-	-		-	-	
054	-	-	-	-	-	-	-	-	-		-	-	
055	-	-	-	-	-	-	-	-	-		-	-	
056	-	-	-	-	-	X	-	-	-	-	-	-	
057	X	-	-	-	-	-	-	-	-	-	-	-	
058	X	X	X	X	X	X	X	X	X		X	X	
059	-	-	-	-	-	-	-	-	-		-	-	
060	-	X	-	-	-	-	-	X	X		X	X	

(*) When required
Generated on 11/26/18:14:55 by DETAIL.SAS/USES: RESPONSE, PRODLIST

APPENDIX III

INFORMED CONSENT DOCUMENT

[redacted] [redacted] [redacted]

INFORMED CONSENT
REPEATED INSULT PATCH TEST

STUDY NO.: [redacted]

PURPOSE

You are invited to participate in this Repeated Insult Patch Test (RIPT), which is a research study to determine if these products can be applied to human skin without causing an allergic reaction. The study will involve a minimum of 100 participants.

STUDY PRODUCT

The study product include or may be components of cosmetics, moisturizers, lipsticks, skin care products, shampoos, shower gel/body wash, antiperspirants/deodorants, disinfectants, antibacterial, fragrances, soaps, sunscreens, fibers, adhesives, antimicrobials (an ingredient used as a preservative), and/or any other products which are intended for and/or may come into contact with human skin. Included is sodium lauryl sulfate (SLS) which is a caustic soap solution used as a control for comparison.

STUDY DURATION

This study consists of 15 visits (16 visits, if required) over 6 weeks, most visits lasting approximately 10-15 minutes. You will receive a schedule of visit dates and instructions.

PROCEDURE

Before you can start the study, the study staff will explain the study and answer any questions you may have. You will be asked to read and sign this form stating that you understand the study procedures. The study staff will begin screening you to see if you meet all study entrance requirements. This study consists of three phases, which include Induction, Rest and Challenge which are explained below.

Each patch received during this study will contain one cosmetic study product. However, more than one patch will be applied with several different cosmetic study products. The dose of the study product will be about 0.2mL, covering a 2cm by 2cm area. You will wear the study product and patch(s) on your back.

Induction: The first three weeks of the study are called the induction phase. During the induction phase you will report to [redacted] on Mondays, Wednesdays and Fridays. At each visit study staff will apply a set of patches to your back. Each patch will be removed 24 and/or 48 hours after application and new patch(s) will be applied at each visit. Your skin will be examined before any study product is applied. The patch(s) applied on Monday and Wednesday will remain on your back for 24 to 48 hours. Patches applied on Friday will be removed on Saturday if 24 hour patch and 48 hour patch(s) applied on Friday will remain in place for 72 hours until you return to [redacted] on the following Monday for patch removal. At each of these induction visits, a clinical evaluator will examine your back to see if you are reacting to any of the products. If you have a strong reaction at the study site (where the study product is applied), the study product will not be applied to that site, but may be applied to another site. The induction period consists of 10 visits.

Rest: During week four of the study, you will begin a rest period during which study product will not be applied to your back and you will not have to report to [redacted]. This rest period will last through weeks four and five.

Challenge: After the rest period is over and week six begins (the final week of the study), you will receive the same products applied on a new area of the back. The study products (with patches) will be put on the part of your back that has not received study product before. During this phase of the study, you will have to return to [redacted] for three more visits. The first visit during the challenge phase you will have your back evaluated and identical patches re-applied. You will return to [redacted] 24 hours after initial challenge patch application for patch removal and skin evaluation. Finally you will return to [redacted] for your final visit, 96 hour after initial challenge patch application, for your final evaluation. If the study doctor/staff determines that it is necessary to make additional evaluations, due to reactions, you will be asked to come back for an additional visit.

[redacted] [redacted] [redacted]

INFORMED CONSENT
REPEATED INSULT PATCH TEST

STUDY NO.: [redacted]

If you are a female of childbearing potential (i.e., not surgically sterile or have not experienced menopause), you must agree to prevent pregnancy throughout this study by using at least one form of accepted birth control [e.g., oral/ injectable/transdermal contraceptive pill, IUD, condom/diaphragm with spermicide, abstinence (no sexual intercourse)].

If you are breastfeeding a child, you will not be permitted to participate in this study. Pregnancy and breastfeeding are prohibited to prevent any unforeseen risk to an unborn child or breast-feeding child.

SUBJECT REQUIREMENTS

You must agree to make all your scheduled visits to [redacted]. You must not apply products such as creams, lotions and moisturizers on or near the test sites. You must avoid sun exposure or the use of tanning beds on your back (including the rest period). You must agree to refrain from swimming during the course of the study. You must agree to minimize water exposure on the patch area while showering or bathing by taking a low tub bath or frontal shower. You will receive written instructions for this study.

POTENTIAL RISKS

Some of the study products may be irritating under certain conditions but the degree of irritation is not expected to be greater than that described below. Individuals participating in this study may experience side effects such as redness, swelling, itching, cracking, peeling, or in rare cases, small blisters or sores. Reactions usually occur only where the study products or patch products (such as the patch tape adhesive) touch the skin. On rare occasions, the reactions may spread beyond the patch. A reaction may result in localized lightening or darkening of the skin, which may persist in an occasional individual. Reactions may be due to either skin irritation or allergy to either study products or patch products (e.g., patch tape adhesive). This study may include taking photographs of part(s) of your back that received study product.

It may be necessary to do additional application (rechallenge) to determine if an allergic reaction has occurred. If you should prove to be allergic, you can expect to react to this product if you encounter it at a later date. Whenever possible, you will be informed as to the identity of the product in order that you may avoid contact with it in the future.

For any significant reactions that may occur as a direct result of your participation in this study, appropriate and reasonable medical treatment will be provided by [redacted], at no cost to you to resolve the immediate problem. Provision of such medical care is not an admission of legal liability or responsibility for the condition being treated. If such reactions occur, [redacted] personnel should be contacted immediately at [redacted] during business hours and at [redacted] at, night or weekends. Extended medical care will not be provided.

POTENTIAL BENEFITS

You may receive no direct benefit from being in this study. However, taking part in this study may benefit society by gaining new knowledge

SIGNIFICANT NEW FINDINGS

You will be informed of any significant new findings that may affect your willingness to continue your participation.

ALTERNATIVE TREATMENT

Since this study is for research only, the only alternative is for you not to participate.

WITHDRAWAL FROM STUDY

Participation in the study is voluntary and you may refuse to participate or may withdraw at any time. Voluntary withdrawal from the study for reasons unrelated to the study or failure to follow test procedures

[redacted] [redacted] [redacted]

INFORMED CONSENT
REPEATED INSULT PATCH TEST

STUDY NO.: [redacted]

will result in some loss of payment based on the number of visits completed. Subjects will be paid $5.00 per visit for early withdrawal. Your participation may also be discontinued at any time without your consent by the study doctor, or the study sponsor(s) (the company(s) that makes the product(s) being evaluated). If you fail to comply with study procedures, your participation may be terminated.

COST

Your participation in the study will not incur any cost to you.

FINANCIAL INCENTIVE

Your participation is voluntary. You may discontinue participation at any time without prejudice. You will be compensated for you participation. A payment of $170.00 will be made only upon completion of all phases of the study. If in the judgment of the investigating personnel, it is best to discontinue your participation in this study due to an adverse experience or severe reaction you will be paid in full for your participation. Voluntary withdrawal from the study for reasons unrelated to the study or failure to follow test procedures will result in some loss of payment based on the number of visits completed. Subjects will be paid $5.00 per visit. Other than the compensation described above, you will not directly benefit from this study. This study is for scientific information. Not participating in the study would be your alternative.

CONFIDENTIALITY AND AUTHORIZATION

[redacted] will protect information about you and your taking part in this research study to the best of our ability. If information about this study is published, your identity will remain confidential. Reports prepared by [redacted] will utilize statistical information only and at no time will your name be used. However, the U.S. Food and Drug Administration (FDA), the sponsor and [redacted] may sometimes inspect the research record and study information of those who take part in this study. By signing this consent form, you are authorizing such access. A court of law could also order research records shown to other people, but that is unlikely. Therefore, absolute confidentiality cannot be guaranteed.

WHO TO CALL

Additional information regarding this research is available either before or during the course of this study. If you have any questions or research related side effect or injury, you may contact the study coordinator, [redacted] during business hours. After business hours the emergency phone number is [redacted].

A copy of this consent form will be given to you.

****

I have read and understand the information given in this consent form. I have had an opportunity to ask questions and my questions have been answered. I voluntarily consent to participate. By signing this form I have not given up any of my legal rights which I would otherwise have as a research subject.

_____	_____	_____	_____
Entry Number	Print Name	Signature	Date

_____ _____

Signature of Person Explaining the Consent Form Date

APPENDIX IV

DERMATOLOGIST SIGNED LETTER

[redacted]

September 4, 2018

[redacted]

Dear Ms. [redacted]

All Dermatologic Safety Studies at [redacted] are conducted under the supervision and coordination of a board-certified dermatologist. [redacted], MD is a board-certified dermatologist and site Medical Director who serves as the Principal Investigator for all Dermatologic Safety studies. As Principal Investigator, Dr. [redacted] follows NIH and Good Clinical Practices (GCP) in his responsibility for delegating authority to trained and qualified personnel, whose credentials are documented on their curriculum vitae (CV) on file with site standard operating procedures. All subject's grading is performed under the supervision of the dermatologist. The dermatologist is responsible for all Clinical Grading Assessments, and for reviewing and signing all laboratory reports.

[redacted]

Director, Dermatologic Safety

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: May 19, 2021

SUBJECT: Zingiber Officinale (Ginger) Water

Solabia Group. 2010. Manufacturing process Vegebios® of Ginger 1.5P (Zingiber Officinale (Ginger) Water).

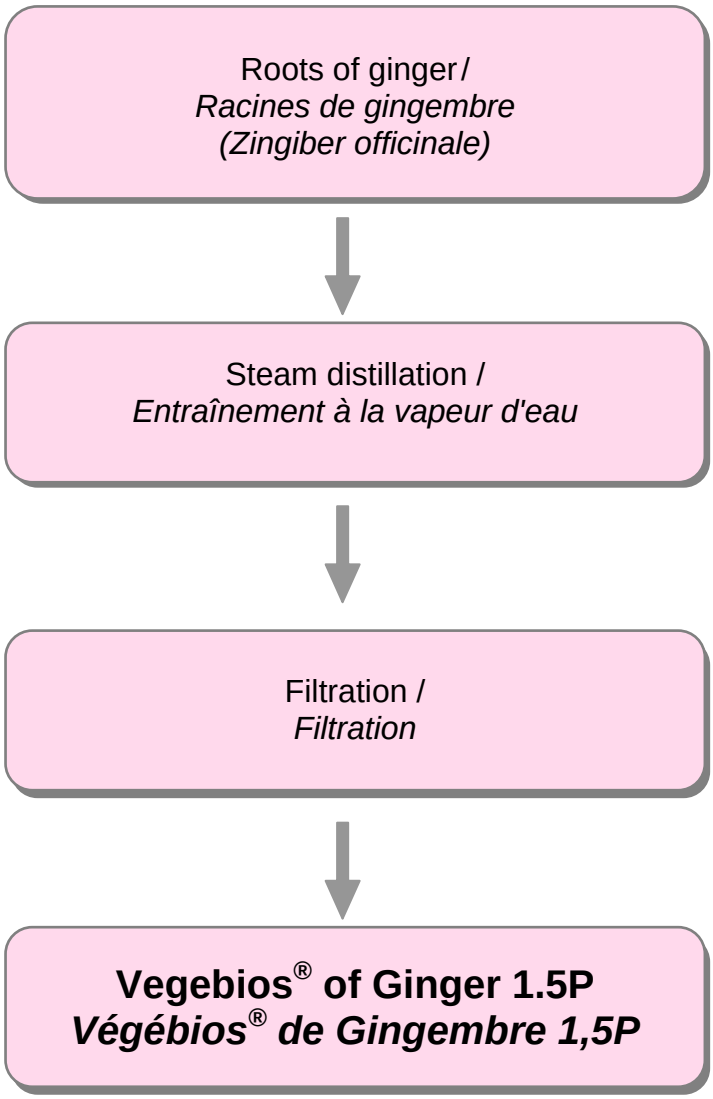
Solabia Group. 2010. Ingredient breakdown Vegebios® of Ginger 1.5P (Zingiber Officinale (Ginger) Water).

MANUFACTURING PROCESS
PROCEDE DE FABRICATION

Vegebios® of Ginger 1.5P
Végébios® de Gingembre 1,5P

Zingiber Officinale (Ginger) Water

Ref. FV602



Produced & Commercialized by CEP - SOLABIA Group
29 Rue Delizy – 93698 Pantin Cedex France
Tel 33 (0)1 48 10 19 40 – Fax 33 (0)1 48 91 18 77 - www.solabia.com

INGREDIENT BREAKDOWN
COMPOSITION CENTESIMALE

Vegebios® of Ginger 1.5P
Végébios® de Gingembre 1,5P

Ref. FV602

CTFA

Zingiber officinale (ginger) water ..... **98.50 %**

Phenoxyethanol ..... **1.50 %**

INCI

Aqua ..... **≥ 98,00 %**

Phenoxyethanol ..... **1.50 %**

Zingiber officinale extract ..... **≤ 0,50 %**

Notes - *Remarques :*

- Because of the natural origin of the raw material, the centesimal composition is susceptible to slight variations.

  En raison de l'origine naturelle des matières premières, la composition centésimale est susceptible de subir une légère variation.

Produced & Commercialized by CEP - SOLABIA Group
29 Rue Delizy – 93698 Pantin Cedex France
Tel 33 (0)1 48 10 19 40 – Fax 33 (0)1 48 91 18 77 - www.solabia.com

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: May 20, 2021

SUBJECT: Zingiber Officinale (Ginger) Root Extract

Anonymous. 2021. Method of manufacture Zingiber Officinale (Ginger) Root Extracts.

May 2021

Method of Manufacture Zingiber Officinale (Ginger) Root Extracts

- water/glycerin 50/50 with preservatives, long maceration of ginger root at room temperature and sterilizing filtration.

-water/glycerin 20/80, preservative free, long maceration of ginger root at room temperature and sterilizing filtration. Can be followed by an evaporation under vacuum.

-sunflower refined oil, hot short maceration of ginger root.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: May 26, 2021

SUBJECT: Zingiber Officinale (Ginger) Root Extract as Part of the Trade Name Mixture SynerCide Asian Fusion

Active Micro Technologies. 2015. Manufacturing flow chart SynerCide Asian Fusion (contains Zingiber Officinale (Ginger) Root Extract).

Active Micro Technologies. 2021. Compositional breakdown SynerCide Asian Fusion (contains Zingiber Officinale (Ginger) Root Extract).

Active Micro Technologies. 2018. Specification SynerCide Asian Fusion (contains Zingiber Officinale (Ginger) Root Extract).

Active Micro Technologies. 2014. Dermal and ocular irritation tests SynerCide Asian Fusion (contains Zingiber Officinale (Ginger) Root Extract).

Active Micro Technologies. 2015. OECD 442C: In chemical skin sensitization SynerCide Asian Fusion (contains Zingiber Officinale (Ginger) Root Extract).

Active Micro Technologies. 2016. OECD 442D. In vitro skin sensitization: SynerCide Asian Fusion (contains Zingiber Officinale (Ginger) Root Extract).

SynerCide Asian Fusion Manufacturing Flow Chart

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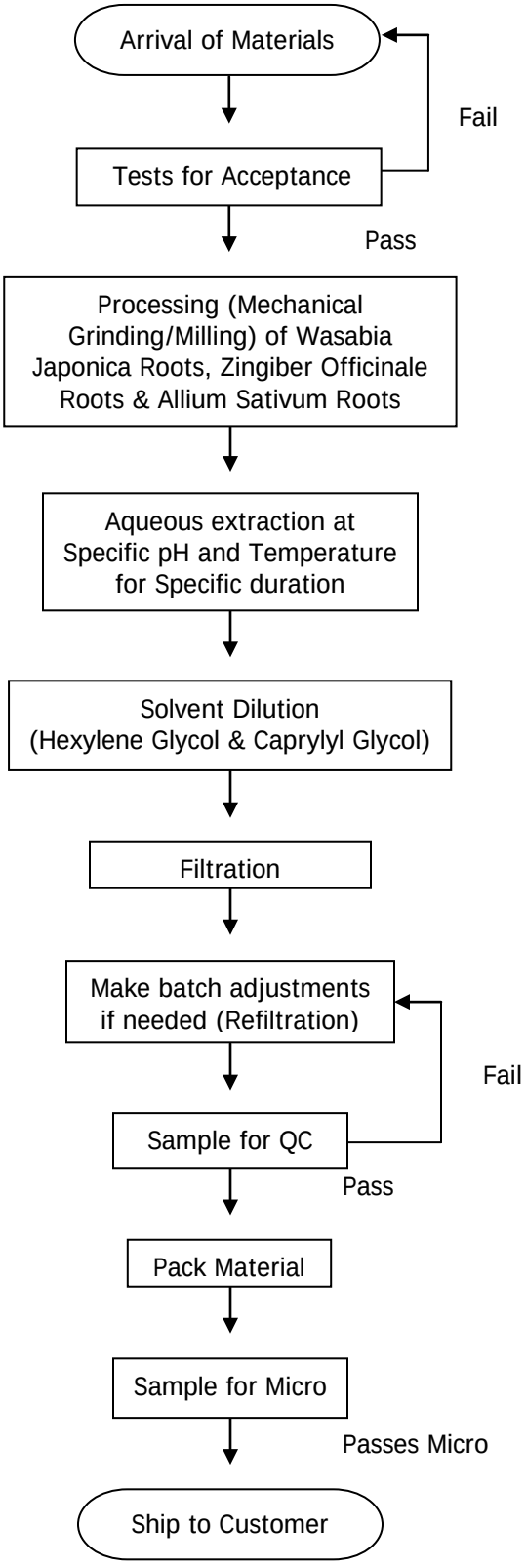
(704) 276-7100 • Fax (704) 276-7101



ACTIVE MICRO TECHNOLOGIES

Compositional Breakdown

107 Technology Drive • Lincolnton, NC 28092
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SynerCide Asian Fusion
Code: M17001

Compositional Breakdown:

Ingredient	%
Hexylene Glycol	28.00 - 32.00
Caprylyl Glycol	12.00 - 17.00
Wasabia Japonica Root Extract	12.00 - 17.00
Zingiber Officinale (Ginger) Root Extract	12.00 - 17.00
Allium Sativum (Garlic) Bulb Extract	12.00 - 17.00
Water	8.00 - 12.00

- **To our knowledge the above material is free of the following list of heavy metals:**
  - **Heavy Metals < 20 ppm (Max.)**
  - **Chromium < 20 ppm (Max.)**
  - **Lead < 10 ppm (Max.)**
  - **Nickel < 10 ppm (Max.)**
  - **Cobalt < 10 ppm (Max.)**
  - **Antimony < 5 ppm (Max.)**
  - **Arsenic < 2 ppm (Max.)**
  - **Mercury < 1 ppm (Max.)**
  - **Cadmium < 1 ppm (Max.)**

Compositional Breakdown

107 Technology Drive • Lincolnton, NC 28092
(704) 276-7100 • Fax (704) 276-7101

Active Micro Technologies hereby confirms that to the best of our knowledge, none of the potential 26 fragrance allergens listed below are present in our finished product or as an intentional component in the raw materials used to manufacture this product. We do not routinely analyze our product for the substances listed below:

ALLERGENS listed in Annex III of EU Cosmetic Regulation(EC) No. 1223/2009	
INCI NAME	CAS Number
Alpha-Isomethyl Ionone	127-51-5
Amyl Cinnamal	122-40-7
Amylcinnamyl Alcohol	101-85-9
Anise Alcohol	105-13-5
Benzyl Alcohol	100-51-6
Benzyl Benzoate	120-51-4
Benzyl Cinnamate	103-41-3
Benzyl Salicylate	118-58-1
Butylphenyl Methylpropional	80-54-6
Cinnamal	104-55-2
Cinnamyl Alcohol	104-54-1
Citral	5392-40-5
Citronellol	106-22-9
Coumarin	91-64-5
Eugenol	97-53-0
Evernia Furfuracea (Treemoss) Extract	90028-67-4
Evernia Prunastri (Oakmoss) Extract	90028-68-5
Farnesol	4602-84-0
Geraniol	106-24-1
Hexyl Cinnamal	101-86-0
Hydroxycitronellal	107-75-5
Hydroxyisohexyl 3-Cyclohexene Carboxaldehyde (Lyral)	31906-04-4
Isoeugenol	97-54-1
Limonene (sum of d, l and dl)	5989-27-5
Linalool	78-70-6
Methyl 2-Octynoate	111-12-6

Compositional Breakdown

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Active Micro Technologies hereby confirms that to the best of our knowledge, none of the pesticides listed below are present in our finished product or as an intentional component in the raw material used to manufacture this product. We do not routinely analyze our product for the substances listed below:

INCI NAME	CAS Number
Alachlor	15972-60-8
Aldrin	309-00-2
Azinphos-methyl	86-50-0
Bromopropylate	18181-80-1
Chlordane (cis and trans)	57-74-9
Chlorfenvinphos	470-90-6
Chlorpyrifos	2921-88-2
Chlorpyrifos-methyl	5598-13-0
Cypermethrin	52315-07-8
DDT	50-29-3
Deltamethrin	52918-63-5
Diazinon	333-41-5
Dichlorvos	62-73-7
Dieldrin	50-57-1
Dithiocarbamates	142-84-7
Endosulfan	115-29-7
Endrin	72-20-8
Ethion	563-12-2
Fenitrothion	122-14-5
Fenvalerate	51630-58-1
Fonofos	944-22-9
Heptachlor	76-44-8
Hexachlorobenzene	118-74-1
Hexachlorocyclohexane	608-73-1
Lindane	58-89-9
Malathion	121-75-5
Methidathion	950-37-8
Parathion	56-38-2
Parathion-methyl	298-00-0
Permethrin	52645-53-1
Phosalone	2310-17-0
Piperonyl butoxide	51-03-6
Pirimiphos-methyl	29232-93-7
Pyrethrins	8003-34-7
Quintozene (sum of 3 items)	82-68-8

ACTIVE MICRO TECHNOLOGIES

107 Technology Drive • Lincolnton, NC 28092
(704) 276-7100 • Fax (704) 276-7101

Specification

Product Name: SynerCide Asian Fusion
Code Number: M17001
CAS #'s: 107-41-5 & 1117-86-8 & 999999-99-4 & 84696-15-1 & 8008-99-9 & 7732-18-5
EINECS #'s: 203-489-0 & 214-254-7 & 310-127-6 & 283-634-2 & 232-371-1 & 231-791-2
INCI Name: Hexylene Glycol & Caprylyl Glycol & *Wasabia japonica* Root Extract & *Zingiber officinale* (Ginger) Root Extract & *Allium sativum* (Garlic) Bulb Extract & Water

Specification	Parameter
Appearance	Clear to Hazy Liquid
Color	Yellow to Light Amber
Odor	Characteristic
Specific Gravity (25^0C)	0.970 – 1.020
Refractive Index (25^0C)	1.3960 – 1.4040
Heavy Metals	< 20 ppm
Lead	< 10 ppm
Arsenic	< 2 ppm
Cadmium	< 1 ppm

DO NOT FREEZE; Store at or near room temperature;
Mix well prior to use; May Sediment upon Standing

Product may change appearance if exposed to cold temperatures during shipment or storage. If this happens, please gently warm to 45-50°C and mix until normal appearance is restored.

ACTIVE MICRO TECHNOLOGIES

Dermal and Ocular Irritation Tests

107 Technology Drive • Lincolnton, NC 28092
(704) 276-7100 • Fax (704) 276-7101

Sample: SynerCide Asian Fusion

Code: M17001

CAS #: 107-41-5 & 1117-86-8 & 999999-99-4 & 84696-15-1 & 8008-99-9 & 7732-18-5

Test Request Form/Submission #: 146

Lot #: 19846

Sponsor: *Active Micro Technologies, LLC; 107 Technology Drive Lincolnton, NC 28092*
Study Director: *Erica Segura*
Principle Investigator: *Meghan Darley*

Test Performed:
In Vitro EpiDerm™ Dermal Irritation Test (EPI-200-SIT)
EpiOcular™ Eye Irritation Test (OCL-200-EIT)

SUMMARY

In vitro dermal and ocular irritation studies were conducted to evaluate whether **SynerCide Asian Fusion** would induce dermal or ocular irritation in the EpiDerm™ and EpiOcular™ model assays.

The product was tested according to the manufacture's protocol. The test article solution was found to be **non-irritating**. Reconstructed human epidermis and cornea epithelial model were incubated in growth media overnight to allow for tissue equilibration after shipping from MatTek Corporation, Ashland, MA. Test substances were applied to the tissue inserts and incubated for 60 minutes for liquid and solid substances in the EpiDerm™ assay and 30 minutes for liquid substances and 90 minutes for solid substances in the EpiOcular™ assay at 37°C, 5% CO_2, and 95% relative humidity (RH). Tissue inserts were thoroughly washed and transferred to fresh plates with growth media. After post substance dosing incubation is complete, the cell viability test begins. Cell viability is measured by dehydrogenase conversion of MTT [(*3-4,5-dimethyl thiazole 2-yl*)], present in the cell mitochondria, into blue formazan salt that is measured after extraction from the tissue. The irritation potential of the test chemical is dictated by the reduction in tissue viability of exposed tissues compared to the negative control.

Under the conditions of this assay, the test article was considered to be **non-irritating**. The negative and positive controls performed as anticipated.

I. Introduction

A. Purpose

In vitro dermal and ocular irritation studies were conducted to evaluate whether a test article would induce dermal or ocular irritation in the EpiDerm™ and EpiOcular™ model assays. MatTek Corporation's reconstructed human epidermal and human ocular models are becoming a standard in determining the irritancy potential of test substances. They are able to discriminate between irritants and non-irritants. The EpiDerm™ assay has accuracy for the prediction of UN GHS R38 skin irritating and no-label (non-skin irritating) test substances. The EpiOcular™ assay can differentiate chemicals that have been classified as R36 or R41 from the EU classifications based on Dangerous Substances Directive (DSD) or between the UN GHS Cat 1 and Cat 2 classifications.

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II. Materials

A. Incubation Conditions: 37°C at 5% CO_2 and 95% relative humidity

B. Equipment: Forma humidified incubator, ESCO biosafety laminar flow hood, Synergy HT Microplate reader; Pipettes

C. Media/Buffers: DMEM based medium; DPBS; sterile deionized H_2O

D. Preparation: Pre-incubate (37°C) tissue inserts in assay medium; Place assay medium and MTT diluent at 4°C, MTT concentrate at -20°C, and record lot numbers of kit components

E. Tissue Culture Plates: Falcon flat bottom 96-well, 24-well, 12-well, and 6-well tissue culture plates

F. Reagents: MTT (1.0mg/mL); Extraction Solution (Isopropanol); SDS (5%); Methyl Acetate

G. Other: Nylon Mesh Circles (EPI-MESH); Cotton tip swabs; 1mL tuberculin syringes; Ted Pella micro-spatula; 220mL specimen containers; sterile disposable pipette tips; Parafilm

III. Test Assay

A. Test System

The reconstructed human epidermal model, EpiDerm™, and cornea epithelial model, EpiOcular™, consist of normal human-derived epidermal keratinocytes which have been cultured to form a multilayer, highly differentiated model of the human epidermis and cornea epithelium. These models consist of organized basal, spinous, and granular layers, and the EpiDerm™ systems also contains a multilayer stratum corneum containing intercellular lamellar lipid layers that the EpiOcular™ system is lacking. Both the EpiDerm™ and EpiOcular™ tissues are cultured on specially prepared cell culture inserts.

B. Negative Control

Sterile DPBS and sterile deionized water are used as negative controls for the EpiDerm™ and EpiOcular™ assays, respectfully.

C. Positive Control

Known dermal and eye irritants, 5% SDS solution and Methyl Acetate, were used as positive controls for the EpiDerm™ and EpiOcular™ assays, respectfully.

D. Data Interpretation Procedure

a. EpiDerm™

An irritant is predicted if the mean relative tissue viability of the 3 tissues exposed to the test substance is reduced by 50% of the mean viability of the negative controls and a non-irritant's viability is > 50%.

b. EpiOcular™

An irritant is predicted if the mean relative tissue viability of the 2 tissues exposed to the test substance is reduced by 60% of the mean viability of the negative controls and a non-irritant's viability is > 40%.

IV. Method

A. Tissue Conditioning

Upon MatTek kit arrival at Active Micro Technologies, LLC the tissue inserts are removed from their shipping medium and transferred into fresh media and tissue culture plates and incubated at 37°C at 5% CO_2 and 95% relative humidity for 60 minutes. After those 60 minutes the inserts are transferred into fresh media and tissue culture plates and incubated at 37°C at 5% CO_2 and 95% relative humidity for an additional 18 to 21 hours.

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B. Test Substance Exposure

a. EpiDerm™

30µL (liquid) or 25mg (solid) of the undiluted test substance is applied to 3 tissue inserts and allowed to incubate for 60 minutes in a humidified incubator (37°C, 5% CO_2, 95% RH).

b. EpiOcular™

Each tissue is dosed with 20µL DPBS prior to test substance dosing. 50µL (liquid) or 50mg (solid) of the undiluted test substance is applied to 2 tissue inserts and allowed to incubate for 90 minutes in a humidified incubator (37°C, 5% CO_2, 95% RH).

C. Tissue Washing and Post Incubation

a. EpiDerm™

All tissue inserts are washed with DPBS, dried with cotton tipped swab, and transferred to fresh media and culture plates. After 24 hours the inserts are again transferred into fresh media and culture plates for an additional 18 to 20 hours.

b. EpiOcular™

Tissue inserts are washed with DPBS and immediately transferred into 5mL of assay medium for 12 to 14 minutes. After this soak the inserts are transferred into fresh media and tissue culture plates for 120 minutes for liquid substances and 18 hours for solid substances.

D. MTT Assay

Tissue inserts are transferred into 300µL MTT media in pre-filled plates and incubated for 3 hours at 37°C, 5% CO_2, and 95% RH. Inserts are then removed from the MTT medium and placed in 2mL of the extraction solution. The plate is sealed and incubated at room temperature in the dark for 24 hours. After extraction is complete the tissue inserts are pierced with forceps and 2 x 200µL aliquots of the blue formazan solution is transferred into a 96 well plate for Optical Density reading. The spectrophotometer reads the 96-well plate using a wavelength of 570 nm.

V. Acceptance Criterion

A. Negative Control

The results of this assay are acceptable if the mean negative control Optical Density (OD_{570}) is ≥ 1.0 and ≤ 2.5 (EpiDerm™) or ≥ 1.0 and ≤ 2.3 (EpiOcular™).

B. Positive Control

a. EpiDerm™

The assay meets the acceptance criterion if the mean viability of positive control tissues expressed as a % of the negative control is ≤ 20%.

b. EpiOcular™

The assay meets the acceptance criterion if the mean viability of positive control tissues is < 60% of control viability.

C. Standard Deviation

Since each irritancy potential is predicted from the mean viability of 3 tissues for EpiDerm™ and 2 tissues for EpiOcular™, the variability of the replicates should be < 18% for EpiDerm™ and < 20% EpiOcular™.

VI. Results

A. Tissue Characteristics

The tissue inserts included in the MatTek EpiDerm™ and EpiOcular™ assay kits were in good condition, intact, and viable.

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B. Tissue Viability Assay

The results are summarized in Figure 1. In no case was the tissue viability ≤ 50% for EpiDerm™ or ≤ 60% for EpiOcular™ in the presence of the test substance. The negative control mean exhibited acceptable relative tissue viability while the positive control exhibited substantial loss of tissue viability and cell death.

C. Test Validity

The data obtained from this study met criteria for a valid assay.

VII. Conclusion

Under the conditions of this assay, the test article substance was considered to be **non-irritating**. The negative and positive controls performed as anticipated.

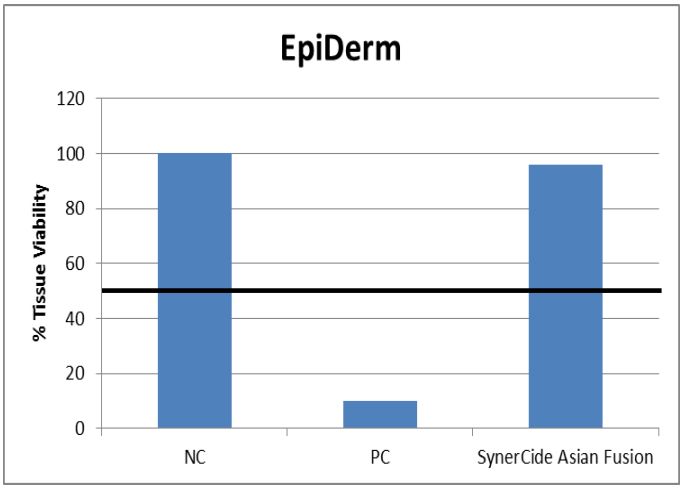

Figure 1: EpiDerm tissue viability

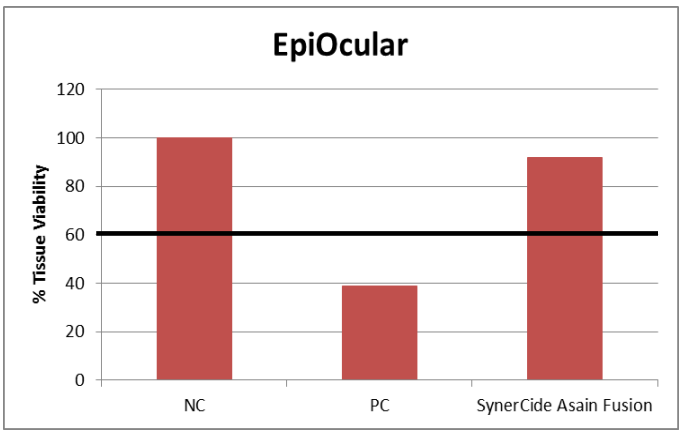

Figure 2: EpiOcular tissue viability

OECD TG 442C: *In Chemico* Skin Sensitization

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(704) 276-7100 • Fax (704) 276-7101

Tradename: SynerCide Asian Fusion

Code: M17001

CAS #: 107-41-5 & 1117-86-8 & 999999-99-4 & 84696-15-1 & 8008-99-9 & 7732-18-5

Test Request Form #: 1427

Lot #: 41590P

Sponsor: *Active Micro Technologies, LLC; 107 Technology Drive Lincolnton, NC 28092*
Study Director: *Erica Segura*
Principle Investigator: *Meghan Darley*

Test Performed:
OECD TG 442C: *In Chemico* Skin Sensitization
Direct Peptide Reactivity Assay (DPRA)

Introduction

A skin sensitizer is a substance that will lead to an allergic response following skin contact[1]. Haptenation is the covalent binding of a hapten, or low-molecular weight substance or chemical, to proteins in the skin. This is considered the prominent mechanism which defines a chemical as a sensitizer. Haptenation is described as a "molecular initiating event" in the OECD Adverse Outcome Pathway (AOP) for skin sensitization which summarizes the key events known to be involved in chemically-induced allergic contact dermatitis[2]. The direct peptide reactivity assay (DPRA) is designed to mimic the covalent binding of electrophilic chemicals to nucleophilic centers in skin proteins by quantifying the reactivity of chemicals towards the model synthetic peptides containing cysteine and lysine. The DPRA is able to distinguish sensitizers from non-sensitizer with 82% accuracy (sensitivity of 76%; specificity of 92%)[3].

This assay was conducted to determine skin sensitization hazard of **SynerCide Asian Fusion** in accordance with European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) and OECD Test Guideline 442C.

Assay Principle

The DPRA is an *in chemico* method which addresses peptide reactivity by measuring depletion of synthetic heptapeptides containing either cysteine or lysine following 24 hours incubation with the test substance. The peptide is a custom material containing phenylalanine to aid in detection. Depletion of the peptide in the reaction mixture is measured by HPLC with gradient elution and UV detection at 220 nm. Cysteine and lysine peptide percent depletion values are then calculated and used in a prediction model which allows assigning the test chemical to one of four reactivity classes used to support the discrimination between sensitizers and non-sensitizers.

1. United Nations Economic Commission (UNECE) (2013) Global Harmonized System of Classification and Labelling of Chemicals (GHS) 5th Revised Edition
2. OECD (2012). The Adverse Outcome Pathway for Skin Sensitization Initiated by Covalent Binding to Proteins. Part 1: Scientific Evidence. Series on Testing and Assessment No. 168
3. EC EURL ECVAM (2012) Direct peptide reactivity assay (DPRA) validation study report; pp 1 -74.

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OECD TG 442C: *In Chemico* Skin Sensitization

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Materials

A.	**Equipment:**	HPLC-UV (Waters Breeze - Waters 2998 Photodiode Array Detector); Pipettes; Analytical balance
B.	**HPLC/Guard Columns:**	Agilent Zorbax SB-C18 2.1mm x 100mm x 3.5µm; Phenomenex Security Guard C18 4mm x 2mm
C.	**Chemicals:**	Trifluoroacetic acid; Ammonium acetate; Ammonium hydroxide; Acetonitrile; Cysteine peptide (Ac-RFAA**C**AA-COOH); Lysine peptide (Ac-RFAA**K**AA-COOH); Cinnamic aldehyde
D.	**Reagents/Buffers:**	Sodium phosphate buffer (100mM); Ammonium acetate buffer (100mM)
E.	**Other:**	Sterile disposable pipette tips

Methods

Solution Preparation:

- 0.667mM Cysteine Peptide in 100mM Phosphate Buffer (pH 7.5)
- 0.667mM Lysine Peptide in 100mM Ammonium Acetate Buffer (pH 10.2)
- 100mM Cinnamic Aldehyde in Acetonitrile
- 100mM **SynerCide Asian Fusion** in Acetonitrile

Reference Controls:

- Reference Control A: For calibration curve accuracy
- Reference Control B: For peptide stability over analysis time of experiment
- Reference Control C: For verification that the solvent does not impact percent peptide depletion

Sample, Reference Control, and Co-Elution Control Preparation:

- Once these solutions have been made they should be incubated at room temperature, protected from light, for 24±2 hours before running HPLC analysis.
- Each chemical should be analyzed in triplicate.

1:10 Ratio, Cysteine Peptide 0.5mM Peptide, 5mM Test Chemical	1:50 Ratio, Lysine Peptide 0.5mM Peptide, 25mM Test Chemical
• 750µL Cysteine Peptide Solution (or 100mM Phosphate Buffer, pH 7.5, for Co-Elution Controls) • 200µL Acetonitrile • 50µL Test Chemical Solution (or Acetonitrile for Reference Controls)	• 750µL Lysine Peptide Solution (or 100mM Ammonium Acetate Buffer, pH 10.2, for Co-Elution Controls) • 250µL Test Chemical Solution (or Acetonitrile for Reference Controls)

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OECD TG 442C:
In Chemico Skin Sensitization

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Calibration Curve:

- Standards are prepared in a solution of 20% Acetonitrile:Buffer
  - For the Cysteine peptide using the phosphate buffer, pH 7.5
  - For the Lysine peptide using the ammonium acetate buffer, pH 10.2

	Standard 1	Standard 2	Standard 3	Standard 4	Standard 5	Standard 6	Standard 7
mM Peptide	0.534	0.267	0.1335	0.0667	0.0334	0.0167	0.000

HPLC Analysis:

- HPLC-UV system should be equilibrated at 30°C with 50% Mobile Phase A (0.1% (v/v) trifluoroacetic acid in water) and 50% Mobile Phase B (0.085% (v/v) trifluoroacetic acid in acetonitrile) for 2 hours
- Absorbance is measured at 220nm
- Flow Conditions:

Time	Flow	%A	%B
0 minutes	0.35 mL/min	90	10
10 minutes	0.35 mL/min	75	25
11 minutes	0.35 mL/min	10	90
13 minutes	0.35 mL/min	10	90
13.5 minutes	0.35 mL/min	90	10
20 minutes	End Run		

Data and Reporting

Acceptance Criteria:

1. The following criteria must be met for a run to be considered valid:
   a. Standard calibration curve should have an $r^2 > 0.99$.
   b. Mean percent peptide depletion values of three replicates for the positive control cinnamic aldehyde should be between 60.8% and 100% for the cysteine peptide and between 40.2% and 69% for the lysine peptide and the maximum standard deviation should be <14.9 for the percent cysteine depletion and <11.6 for the percent lysine depletion.
   c. Mean peptide concentration of reference controls A should be 0.50±0.05mM and the coefficient of variable of the peptide peak areas for reference B and C in acetonitrile should be <15.0%.

2. The following criteria must be met for a test chemical's results to be considered valid:
   a. Maximum standard deviation should be <14.9 for percent cysteine depletion and <11.6 for percent lysine depletion.
   b. Mean peptide concentration of the three reference control C should be 0.50±0.05mM.

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OECD TG 442C:
***In Chemico* Skin Sensitization**

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Prediction Model:

Cysteine 1:10/Lysine 1:50 Prediction Model		
Mean of Cysteine and Lysine % Depletion	**Reactivity Class**	**Prediction**
0% < Mean % Depletion < 6.38%	Minimal Reactivity	Non-sensitizer
6.38% < Mean % Depletion < 22.62%	Low Reactivity	Sensitizer
22.62% < Mean % Depletion < 42.47%	Moderate Reactivity	Sensitizer
42.47% < Mean % Depletion < 100%	High Reactivity	Sensitizer

If co-elution occurs with the lysine peptide, than the cysteine 1:10 prediction model can be used:

Cysteine 1:10 Prediction Model		
Mean of Cysteine and Lysine % Depletion	**Reactivity Class**	**Prediction**
0% < Cys % Depletion < 13.89%	Minimal Reactivity	Non-sensitizer
13.89% < Cys % Depletion < 23.09%	Low Reactivity	Sensitizer
23.09% < Cys % Depletion < 98.24%	Moderate Reactivity	Sensitizer
98.24% < Cys % Depletion < 100%	High Reactivity	Sensitizer

Results and Discussion

The data obtained from this study met criteria for a valid assay and the controls performed as anticipated.

Percent peptide depletion is determined by the following equation:

$$Percent\ Peptide\ Depletion = \left[1 - \left(\frac{Peptide\ Peak\ Area\ in\ Replicate\ Injection}{Mean\ Peptide\ Peak\ Area\ in\ Reference\ Controls\ C}\right)\right] \times 100$$

Based on HPLC-UV analysis of **SynerCide Asian Fusion (code M17001)** we can determine that this product is not a sensitizer and will not cause allergic contact dermatitis. The Mean Percent Depletion of Cysteine and Lysine was 1.89% causing minimal reactivity in the assay giving us the prediction of a non-sensitizer.

ACTIVE MICRO TECHNOLOGIES

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OECD TG 442D: *In Vitro* Skin Sensitization

Tradename: SynerCide Asian Fusion

Code: M17001

CAS #: 107-41-5 & 1117-86-8 & 999999-99-4 & 84696-15-1 & 8008-99-9 & 7732-18-5

Test Request Form #: 1428

Lot #: 41590

Sponsor: *Active Micro Technologies, LLC; 107 Technology Drive Lincolnton, NC 28092*
Study Director: *Erica Segura*
Principle Investigator: *Meghan Darley*

Test Performed:
OECD TG 442D: In Vitro Skin Sensitization
ARE-Nrf2 Luciferase Test Method

Introduction

Skin sensitization refers to an allergic response following skin contact with the tested chemical, as defined by the United Nations Globally Harmonized System of Classification and Labelling of Chemicals[1]. Substances are classified as skin sensitizers if there is evidence in humans that the substance can lead to sensitization by skin contact or positive results from appropriate tests, both *in vivo* and *in vitro*. Utilization of the KeratinoSens™ cell line allows for valid *in vitro* testing for skin sensitization.

This assay was conducted to determine skin sensitization potential of **SynerCide Asian Fusion** in accordance with the UN GHS.

Assay Principle

The ARE-Nrf2 luciferase test method addresses the induction of genes that are regulated by antioxidant response elements (ARE) by skin sensitizers. The Keap1-Nrf2-ARE pathways have been shown to be major regulator of cytoprotective responses to oxidative stress or electrophilic compounds. These pathways are also known to be involved in the cellular processes in skin sensitization. Small electrophilic substances such as skin sensitizers can act on the sensor protein Keap1 (Kelch-like ECH-associated protein 1), by covalent modification of its cysteine residue, resulting in its dissociation from the transcription factor Nrf2 (nuclear factor-erythroid 2-related factor 2). The dissociated Nrf2 can then activate ARE-dependent genes such as those coding for phase II detoxifying enzymes.

The skin sensitization assay utilizes the KeratinoSens™ method which uses an immortalized adherent human keratinocyte cell line (HaCaT cell line) that has been transfected with a selectable plasmid to quantify luciferase gene induction as a measure of activation of Keap1-Nrf2-antioxidant/electrophile response element (ARE). This test method has been validated by independent peer review by the EURL-ECVAM. The addition of a luciferin containing reagent to the cells will react with the luciferase produced in the cell resulting in luminescence which can be quantified with a luminometer.

1. United Nations (UN) (2013). Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Fifth revised edition, UN New York and Geneva, 2013

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OECD TG 442D: *In Vitro* Skin Sensitization

Materials

A. Incubation Conditions:	37°C at 5% CO_2 and 95% relative humidity (RH)
B. Equipment:	Humidified incubator; Biosafety laminar flow hood; Microplate Reader; Pipettes
C. Cell Line:	KeratinoSens™ by Givaudan Schweiz AG
D. Media/Buffers:	Dulbecco's Modified Eagle Medium (DMEM); Fetal Bovine Serum (FBS); Phosphate Buffered Saline (PBS); Geneticin
E. Culture Plate:	Flat bottom 96-well tissue culture treated plates
F. Reagents:	Dimethyl Sulfoxide (DMSO); Cinnamic Aldehyde; ONE-Glo Reagent; 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT); sodium lauryl sulfate (SLS)
G. Other:	Sterile disposable pipette tips; wash bottles

Methods

KeratinoSens™ were into seeded four 96-well tissue culture plates and allowed to grow to 80 – 90% confluency in DMEM containing 10% FBS and 500µg/mL G418 geneticin. Twelve test concentrations of **SynerCide Asian Fusion** were prepared in DMSO with a concentration range from 0.98 – 2000 µM. These 12 concentrations were assayed in triplicate in 2 independently performed experiments. The positive control was cinnamic aldehyde for which a series of 5 concentrations prepared in DMSO had final test concentrations of 4 – 64µM. The negative control was a 1% test concentration of DMSO.

24 hour post KeratinoSens™ seeding, the culture media was removed and replaced with fresh media containing 10% FBS without G418 geneticin. 50 µL of the above described test concentrations was added to the appropriate wells. The treated plates were then incubated for 48 hours at 37°C in the presence of 5% CO_2 and 95% relative humidity. After treatment incubation was complete the media was removed and the wells were washed with PBS 3 times.

One of the four plates was used for a cytotoxicity endpoint, where MTT was added to the wells and incubated for 4 hours at 37°C in the presence of 5% CO_2. SLS was then added to the wells and incubated overnight at room temperature. A spectrometer measured the absorbance at 570 nm. The absorbance values (optical density) were then used to determine the viability of each well by comparing the optical density of each test material treated well to that of the solvent control wells to determine the IC_{50} and IC_{30} values.

The remaining 3 plates were used in the luciferase induction endpoint of the assay. 100 µL of Promega's ONE-Glo Reagent was added to 100 µL of fresh media containing 10% FBS without geneticin. Cells were incubated for 5 minutes to induce cell lysis and release luciferin into the media. Plates were read with a luminometer and $EC_{1.5}$ and maximum response (I_{max}) values were obtained.

Data and Reporting

Acceptance Criteria:

1. Gene induction obtained with the positive control, cinnamic aldehyde, should be statistically significant above the threshold of 1.5 in at least one of the tested concentrations (from 4 to 64 µM).
2. The EC1.5 value should be within two standard deviations of the historical mean and the average induction in the three replicates for cinnamic aldehyde at 64 µM should be between 2 and 8.
3. The average coefficient of variability of the luminescence reading for the negative (solvent) control DMSO should be below 20% in each experiment.

ACTIVE MICRO TECHNOLOGIES

OECD TG 442D:
***In Vitro* Skin Sensitization**

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A KeratinoSens™ prediction is considered positive if the following conditions are met:

1. The Imax is higher than 1.5-fold and statistically significantly higher as compared to the solvent (negative) control
2. The cellular viability is higher than 70% at the lowest concentration with a gene induction above 1.5 fold (i.e., at the EC1.5 determining concentration)
3. The $EC_{1.5}$ value is less than 1000 µM (or < 200 µg/ml for test chemicals with no defined MW)
4. There is an apparent overall dose-response for luciferase induction

Results

Compound	Classification	$EC_{1.5}$ (µM)	IC_{50}	I_{max}
Cinnamic aldehyde	Sensitizer	19	289.19 µM	31.6
DMSO	Non-Sensitizer	No Induction	243.24 µM	1.2
SynerCide Asian Fusion	Non-Sensitizer	No Induction	> 1000 µM	0.4

Table 1: Overview of KeratinoSens™ Assay Results

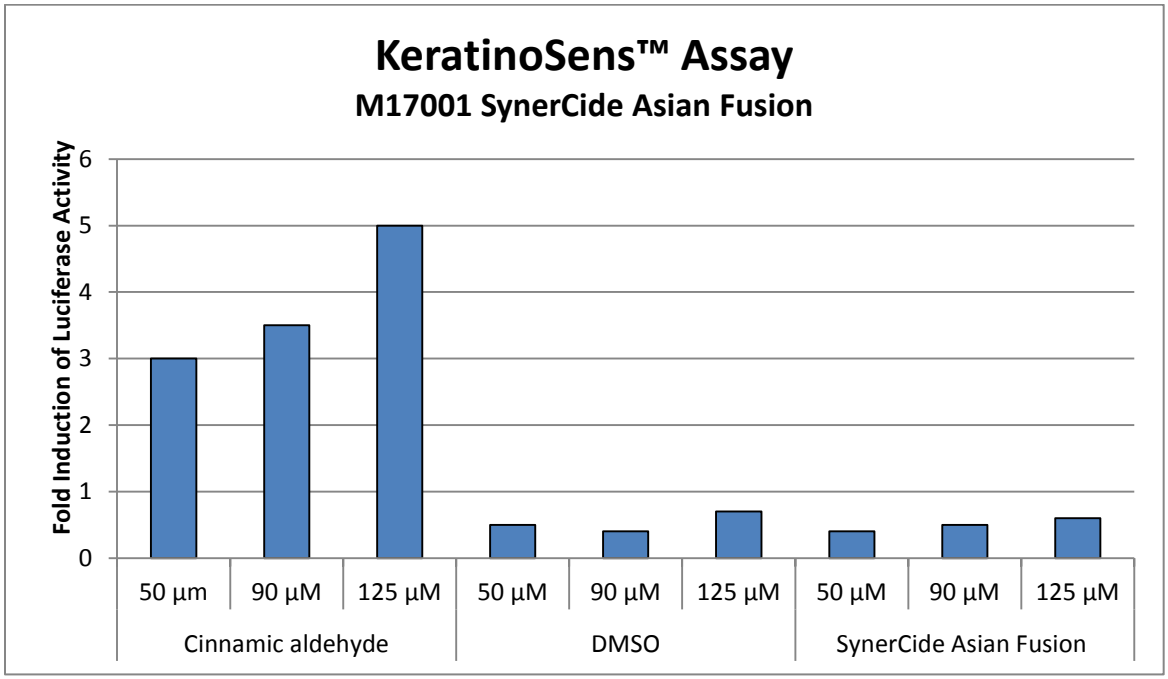

Figure 1: Fold Induction of Luciferase

Discussion

As shown in the results, **SynerCide Asian Fusion (code M17001)** was not predicted to be a skin sensitizer based on the KeratinoSens™ ARE-Nrf2 Luciferase Test Method as there was not a significant increase in luciferase expression. It can be concluded that **SynerCide Asian Fusion** can be safely used in cosmetics and personal care products at typical use levels.

Concentration of Use by FDA Product Category – Ginger-Derived Ingredients*

Zingiber Officinale (Ginger) Extract
Zingiber Officinale (Ginger) Leaf Cell Extract
Zingiber Officinale (Ginger) Rhizome Extract
Zingiber Officinale (Ginger) Root
Zingiber Officinale (Ginger) Root Extract
Zingiber Officinale (Ginger) Root Juice
Zingiber Officinale (Ginger) Root Oil
Zingiber Officinale (Ginger) Root Powder
Zingiber Officinale (Ginger) Water

Ingredient	Product Category	Maximum Concentration of Use
Zingiber Officinale (Ginger) Extract	Hair conditioners	0.0009%
Zingiber Officinale (Ginger) Extract	Tonics, dressings, and other hair grooming aids	0.000042%
Zingiber Officinale (Ginger) Root Extract	Bath oils, tablets, and salts	0.0000033%
Zingiber Officinale (Ginger) Root Extract	Other bath preparations	0.001-0.0007%
Zingiber Officinale (Ginger) Root Extract	Colognes and toilet waters	0.001%
Zingiber Officinale (Ginger) Root Extract	Other fragrance preparations	0.1%
Zingiber Officinale (Ginger) Root Extract	Hair conditioners	0.0006-0.018%
Zingiber Officinale (Ginger) Root Extract	Hair sprays Pump spray	0.0019%
Zingiber Officinale (Ginger) Root Extract	Shampoos (noncoloring)	0.0001-0.002%
Zingiber Officinale (Ginger) Root Extract	Tonics, dressings, and other hair grooming aids	0.009%
Zingiber Officinale (Ginger) Root Extract	Hair rinses (coloring)	0.0016%
Zingiber Officinale (Ginger) Root Extract	Foundations	0.0016%
Zingiber Officinale (Ginger) Root Extract	Lipstick	0.0072-0.02%
Zingiber Officinale (Ginger) Root Extract	Bath soaps and detergents	0.0001-0.00028%
Zingiber Officinale (Ginger) Root Extract	Other personal cleanliness products	0.0001%
Zingiber Officinale (Ginger) Root Extract	Aftershave lotions	0.0001%
Zingiber Officinale (Ginger) Root Extract	Shaving cream Aerosol – bag valve	0.012%
Zingiber Officinale (Ginger) Root Extract	Shaving soap	0.0004%
Zingiber Officinale (Ginger) Root Extract	Other shaving preparations	0.0001%
Zingiber Officinale (Ginger) Root Extract	Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	0.0001-0.1%
Zingiber Officinale (Ginger) Root Extract	Face and neck products Not spray	0.08-0.2%
Zingiber Officinale (Ginger) Root Extract	Body and hand products Not spray	0.0001-0.0012%
Zingiber Officinale (Ginger) Root Extract	Moisturizing products Not spray	0.024-0.2%
Zingiber Officinale (Ginger) Root Extract	Paste masks and mud packs	0.0008-0.22%
Zingiber Officinale (Ginger) Root Extract	Other skin care preparations	0.0005-0.08%
Zingiber Officinale (Ginger) Root Oil	Bath oils, tablets, and salts	0.001%
Zingiber Officinale (Ginger) Root Oil	Other fragrance preparations	0.00032%, 100%**

Zingiber Officinale (Ginger) Root Oil	Hair conditioners	0.004%
Zingiber Officinale (Ginger) Root Oil	Shampoos (noncoloring)	0.004%
Zingiber Officinale (Ginger) Root Oil	Deodorants Not spray	 0.000046-0.0021%
Zingiber Officinale (Ginger) Root Oil	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.001%
Zingiber Officinale (Ginger) Root Oil	Body and hand products Not spray Pump spray	 0.001-0.003% 0.001%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

**Essential oil: diluted for use a few drops used per teaspoon of carrier oil

Information collected in 2020
Table prepared January 25, 2021

2021 FDA VCRP – Ginger-Derived Ingredients

Zingiber Officinale (Ginger) Extract – total = 4 uses

Deodorants (underarm)	1
Other Personal Cleanliness Products	1
Body and Hand (exc shave)	1
Paste Masks (mud packs)	1

Zingiber Officinale (Ginger) Rhizome Extract – total = 1 use

Moisturizing	1

Zingiber Officinale (Ginger) Leaf Cell Extract – No reported uses

Zingiber Officinale (Ginger) Root - No reports uses

Zingiber Officinale (Ginger) Root Extract – total = 207 uses

Bath Oils, Tablets, and Salts	1
Eye Lotion	1
Other Eye Makeup Preparations	2
Cologne and Toilet waters	1
Hair Conditioner	24
Shampoos (non-coloring)	22
Tonics, Dressings, and Other Hair Grooming Aids	8
Wave Sets	1
Other Hair Preparations	7
Foundations	2
Lipstick	2
Makeup Bases	2
Other Makeup Preparations	2
Dentifrices	1
Other Oral Hygiene Products	1
Bath Soaps and Detergents	6
Deodorants (underarm)	1
Beard Softeners	1
Cleansing	12
Face and Neck (exc shave)	27
Body and Hand (exc shave)	13
Moisturizing	38
Night	1
Paste Masks (mud packs)	8
Skin Fresheners	4
Other Skin Care Preps	19

Zingiber Officinale (Ginger) Root Juice – No reported uses

Zingiber Officinale (Ginger) Root Oil – total = 123 uses

Bath Oils, Tablets, and Salts	6
Perfumes	1
Other Fragrance Preparation	13
Hair Conditioner	2
Shampoos (non-coloring)	5
Tonics, Dressings, and Other Hair Grooming Aids	2
Other Hair Preparations	4
Face Powders	1
Lipstick	2
Bath Soaps and Detergents	15
Deodorants (underarm)	5
Other Personal Cleanliness Products	1
Beard Softeners	2
Other Shaving Preparation Products	2
Cleansing	7
Face and Neck (exc shave)	3
Body and Hand (exc shave)	15
Moisturizing	20
Paste Masks (mud packs)	1
Skin Fresheners	3
Other Skin Care Preps	13

Zingiber Officinale (Ginger) Root Powder – total = 4 uses

Other Oral Hygiene Products	1
Bath Soaps and Detergents	2
Body and Hand (exc shave)	1

Zingiber Officinale (Ginger) Water – total = 2 uses

Other Bath Preparations	1
Shampoos (non-coloring)	1